FORMULATION AND EVALUATION OF

INDOMETHACIN EXTENDED RELEASE PELLETS

Dissertation

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF INDOMETHACIN EXTENDED RELEASE PELLETS**" submitted by **Mr**. **MADHU KRISHNA. CHITLURI** to Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year 2011-2012.

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ABBREVATIONS

GIT	Gastrointestinal tract
hr	hour
sec	second
mg	milligram
nm	nanometer
µm	micrometer
W/V	Wight / volume
g/cc	gram / cubic centimeter
#	Mesh size
RPM	Rotation per minute
USP	United states Pharmacopoeia
ml	milliliter
min	minute
gm	gram
ADME	Absorption, Distribution, Metabolism & Excretion
mm	millimeter
W/W	Weight / Weight
µg/ml	microgram / milliliter
^0c	Degree Celsius
%	Percentage

CONTENTS

1. INTRODUCTION

1.1 ORAL DRUG DELIVERY [1]:

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the dosage form is complete, plasma drug concentration decline according to drug's pharmacokinetic profile. Eventually, plasma drug concentration fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate release dosage forms.

1.2 MODIFIED DRUG DELIVERY:

The term modified release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized. Several types of modified-release drug products are recognized.

Modified release delivery systems may be divided conveniently in to four categories:

- **A. Delayed release**
- **B. Controlled release**
  - **i. Sustained release**
  - **ii. Extended release**
- **C. Site specific targeting**
- **D. Receptor targeting**

A. Delayed Release:

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated in to a single dosage form. Examples of delayed release systems included repeat action tablets, capsules and enteric-coated tablets where timed release is achieved by barrier coating.

B. Controlled release systems:

These systems include any drug delivery systems that achieves slow release of drug over an extended period of time and also can provide some control, where this be of a temporal or spatial nature, or both, drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

i) **Sustained release:**

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

ii) **Extended release:**

Pharmaceutical dosage forms that release the drug slower than normal manner and necessarily reduce the dosage frequency by two folds.

C. Site specific targeting:

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to the effected organ or tissue.

D. Receptor targeting:

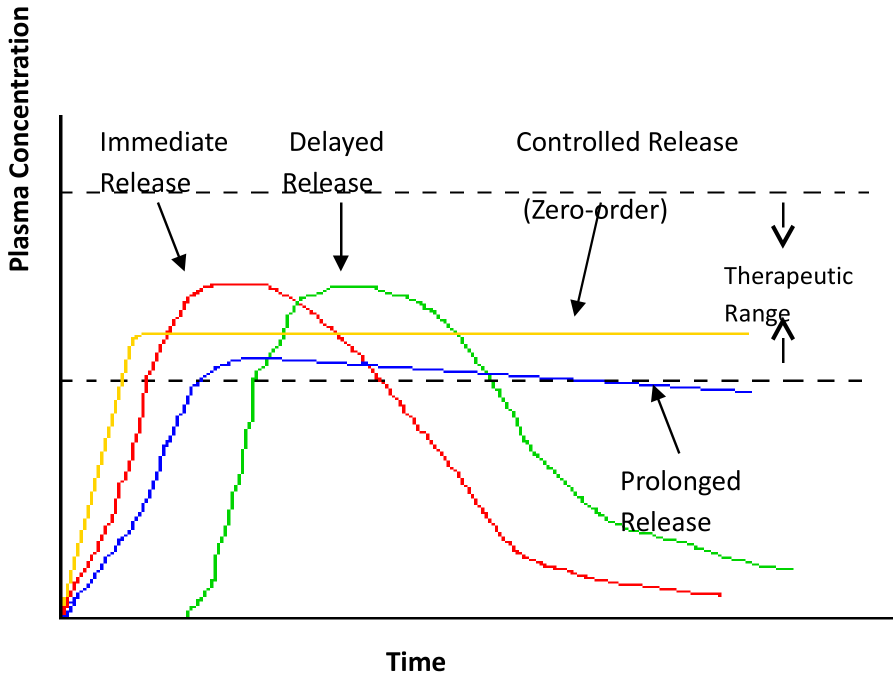
These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue.

1.3 EXTENDED RELEASE DOSAGE FORMS [2]:

Dosage forms which can reduce at least a two fold reduction in dosing frequency as compared to the drug presented in a conventional form, such as solution or a prompt releasing conventional solid dosage form are termed as extended release dosage forms.

These products are formulated to make the contained medicament available over an extended period of time after administration within its therapeutic range and hence reduction in dosing frequency as compared to the conventional dosage forms.

Comparison of different types of modified release dosage formulations as per plasma concentration vs. time can be explained by the following figure. (1)



ADVANTAGES AND DISADVANTAGES OF ORAL EXTENDED RELEASE DOSAGE FORMS

All sustained release dosage forms have a common goal of improving the drug therapy compared to that achieved by their non sustained counter parts.

Advantages

- Avoid patient compliance problems
- Employ less quantity drug.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Reduce dosing frequency and fluctuation of therapeutic plasma concentration
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.

- Improves efficiency in treatment
- Cures or control conditions more promptly.
- Improves control of condition i.e., reduces fluctuations in drug level.
- Improves bioavailability of some drugs.
- Makes use of special effects in sustained release aspirin for morning relief of arthritis by dosing before bedtime.
- Economy

Disadvantages

- Dose dumping, toxicity can occur if system fails.
- Reduced potential for accurate dose adjustments.
- Need for additional patient education.
- Does not permit the prompt termination of drug therapy.
- Cannot exercise any control once the dosage form is administered.

1.3.1 TYPES OF EXTENDED RELEASE PRODUCTS:

(a) Diffusion Controlled Products

In these a water-insoluble polymer which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Both diffusion and dissolution processes are involved. In `reservoir' devices, a core of drug is encapsulated with in a polymer coat, and in `matrix' systems, the drug is dispersed throughout the matrix. Cellulose derivatives are commonly used in the reservoir types, while the matrix material may be plastics, e.g. methylacrylate-methyl methacrylate, polyvinyl chloride, hydrophilic polymers such as cellulose derivatives or fatty compounds including carnauba wax. Examples of this type of formulation include Agon SR, Kapanol and Slow-K. [2,3]

(b) Dissolution Controlled Products

The rate of release of the drug (and there by availability for absorption) is controlled by slowly erodible/ soluble polymers or by micro encapsulation of drugs with slowly soluble polymers. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thickness of the coat and its composition, the rate of drug release can be controlled. Some preparations contain a fraction of the total dose as an immediate-release component to provide an immediate dose soon after administration.

The pellet dosage forms of diffusion or dissolution controlled products can be encapsulated or prepared as a tablet. Encapsulated pellet products have an advantage that the onset of absorption is less sensitive to stomach emptying. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating extended-release tablet formulations. An example of this type of product is Fefol [4].

(c) Erosion Products

The release of drug from these products is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion. An example of this formulation is Sinemet CR. This product, some patients may experience a delayed onset of action after the morning dose, compared to conventional levodopa tablets, because of the delayed release of the drug.

(d) Osmotic pump systems

The rate of release of drug from this drug delivery system is maintained by the constant inflow of water across a semi permeable membrane into a reservoir, which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which dissolved drug is pumped at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within limits yielding relatively constant blood concentrations. The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. The rate of release can be modified by altering the osmotic agent and the size of the hole. An example of this type of product is ALZET. [3,4]

Ion exchange systems

Some drugs can be bound to ion exchange resins and, when ingested, the release of drug is determined by the ionic environment within the gastrointestinal tract. Examples of this type of product are Duromine containing the basic drug phentermine complexed onto an anionic resin [4].

1.3.2 FACTORS TO BE CONSIDER IN DESIGN OF EXTENDED RELEASE PRODUCTS:

To successfully design extended release drug delivery system for a given drug, information about drug like,

- The properties of the drug, its behavior in biological systems, its biological half life is essential.
- The Absorption, Distribution, Metabolism and Elimination (ADME) characteristics of the drug will enable the development of mathematical models to adequately describe the transit of the drug in the system.
- The relationship between the absorption and the blood concentration.
- The desired profile of therapeutic action with these kinds of segments like rapid rise, constant tissue level and rapid concentration.
- Information related to the tendency of the drug to get accumulated or bound to plasma proteins and any body tissue.
- The route of administration, the dose and the ultimate pharmacological action.
- Various physical and chemical properties of the drug.

1.3.3 MECHANISM OF EXTENDED RELEASE:

The rate of release of a drug dispersed as a solid in an inert matrix has been described by Higuchi. In this model it is assumed that the solid drug is dissolved from the surface layer of device first and this layer becomes exhausted of the drug; the next layer begins to get depleted by dissolution and diffusion through the matrix, to the external solution. In this fashion interface between the regions containing dissolved drug and that containing the dispersed drug moves to the interior as a front[2,3].

The assumptions which are made in deriving the mathematical models are as follows:

- A pseudo steady state is maintained during the release.
- The total amount of drug present per unit volume in the matrix, C_0 is substantially greater than the saturation solubility of drug per unit volume in the matrix Cs
- The release media is the perfect sink at all times.
- Drug particles are much smaller in diameter than the average distance of diffusion.
- The diffusion coefficient remains constant.
- No interaction occurs between drug and the matrix.

Schematic representation of the physical model used for a planar slab matrix diffusion device based on the above assumptions, the change in the amount of the drug released per unit area, dM with a change in the depleted zone thickness dh, is

$$dM = Codh – (Cs/2)\ dh \text{ ------------- (a)}$$

Where, Co and Cs is the drug present per unit volume and saturation solubility respectively.

$$dM = (Dm.\ Cs / h)\ dt \text{ ---------------- (b)}$$

Where, Dm is the diffusion coefficient of the matrix.

If the equation a and b are equated, and solved for h , and that value of 'h' was substituted back in to the integrated form of equation(b) an equation for M is obtained.

$$M = [Cs\ Dm\ (2Co - Cs)\ t]\ 1/2 \text{ ------------(c)}$$

Similarly, a Drug release from a porous granular matrix is described by,

$$M = [C\alpha\ Ds\ (\varepsilon / T)\ (2Co – \varepsilon\ C\alpha)\ t]1/2 \text{ --------- (d)}$$

Where, ε is porosity of matrix,

T is tortuosity,

Cα is the solubility of drug in the release medium,

Ds is diffusion co-efficient of drug in the release medium.

For the purposes of the data treatment, equation (b) and (c) are conveniently reduced to

$$M = Kt1/2$$

Where K is a constant, so that a plot an amount of drug released versus square root of time should be linear if the release of drug is diffusion controlled.

1.4 MULTI PARTICULATE DRUG DELIVERY SYSTEM:

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet [5,6].

Multiparticulates are discrete particles that make up a multiple unit system. They provide many advantages over single-unit systems because of their small size. Multi-particulates are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation. Recently much emphasis is being laid on the development of multiparticulate dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying [7,8].

There are many reasons for formulating a drug as a multiparticulate system for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Multiparticulate systems show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. After disintegration which occurs within a few minutes often even within seconds, the individual subunit particles pass rapidly through the GI tract. If these subunits have diameters of less than 2 mm, they are able to leave the stomach continuously, even if the pylorus is closed. These results in lower intra and inter individual variability in plasma levels and bioavailability.

1.4.1 SOME APPROACHES TO MULTIPARTICULATE FORMULATION:

The site-specific delivery of drugs to the colon has implications in a number of therapeutic areas, which include topical treatment of colonic disorders such as Crohn's disease, ulcerative colitis, constipation, colorectal cancer, spastic colon and irritable bowel syndrome. Multiparticulates approaches tried for colonic delivery includes formulations in the form of pellets, granules, microparticles and nanoparticles. Because of their smaller particle size compared to single unit dosage forms these systems are capable of passing through the GI tract easily leading to low inter and intra subject variability. Moreover, multiparticulate systems are to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption. Multiparticulates may be prepared by several methods. Different methods require different processing conditions and produce multiparticulates of distinct qualities. Some of these methods may be broadly classified as:

- Pelletization
- Granulation
- Spray drying
- Spray congealing

Drug particles may be entrapped within the multiparticulates or layered around them. Subsequently, these multiparticulates may be modified in many ways to achieve the desired drug release profile. One approach to the modification of drug release profile in multiparticulates is to coat them. Reasons for the application of coating onto multiparticulates are to obtain functional coats, provide chemical stability, improve physical characteristics and enhance patient acceptance. Coats are formed from various polymeric coating materials broadly classified as aqueous polymer dispersions, polymer solutions, molten polymers and dry powders. Depending on the type of coating material used, functions such as sustained release, targeted release, delayed release and pulsatile release can be achieved.

The most common method used for the application of coating onto multiparticulates is air suspension coating. Other methods include compression coating, solvent evaporation, co-acervation and Interfacial complexation. It is also possible to form coated multiparticulates by spray drying and spray congealing.

A multiparticulate composition may allow controlled release of the drug over a wide range of release rates and permit the release rate to be set at a predetermined rate, such a formulation may be formed using a melt-congeal process which maintains the crystallinity of the drug during the melt congeal process [7,8,9,10].

1.4.2 MECHANISM OF DRUG RELEASE FROM MULTI-PARTICULATES:

The mechanism of drug release from multiparticulates occurs in the following ways:

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, there by releasing the drug contained within the particle.

Osmosis

In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating [11].

1.5 PELLETS:

Figure No: 2

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm and are intended usually for oral administration. Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today[12,13,14].

The most common advantages of Pelletization are [15,16,17,18,19,20]:

- Improved appearance of the product and the core is pharmaceutically elegant.
- Pelletization offers flexibility in dosage form design and development.
- Pellets are less susceptible to dose dumping.
- It reduces localized concentration of irritative drugs.
- It improves safety and efficacy of a drug.
- Pellets offer reduced variation in gastric emptying rate and transit time.
- Pellets disperse freely in GIT and invariably maximize drug absorption and also reduce peak plasma fluctuation.
- Pellets ensure improved flow properties in formulation development.
- The coating of pellets can be done with different drugs to enable a controlled release rate of the formulations.
- Pellets minimize intra and inter subject variability profiles, unlike the single unit conventional dosage form.
- Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area to volume ratio.
- Pellets composed of different drugs can be blended and formulated in a single dosage form.
- Even pellets with different release rates of the same drug can be supplied in a single dosage form.
- Pellets can be divided into different dose strengths without formulation and process changes.
- They can be blended to deliver different incompatible agents simultaneously.
- They provide different release rates at same or different places of gastro intestinal tract.

1.5.1 PELLET FORMATION AND GROWTH:

The mechanism of pellet formation and growth, the following steps were proposed:

- Nucleation
- Coalescence
- Layering

- Abrasion transfer.

Nucleation

Nucleation is a common stage in all pelletization/granulation processes and occurs whenever a powder is wetted with liquid. The primary particles are drawn together to form three phase air wetted liquid nuclei and are attached together by liquid bridges, which are pendular in nature. The bonding strength is improved by reduction of particle size. The sizes of primary particles, moisture content, viscosity of binding particles, wet ability of substrate and the processing conditions, such as tumbling and drying rates, influence the size, rate and the extent of nuclear formation. Both mass and number of nuclei in the system changes as a function of time, which is an important feature of nucleation [13,21,22].

Nucleation followed by a transition phase and the growth mechanism affecting the transition region are coalescence and layering.

Coalescence

Coalescence is defined as the formation of large sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface. Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering is a slow growth mechanism and involves a successive addition of fragments and fines on an already formed nucleus [22].

Layering

In the layering step, the number of particles remains same but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter. The fines and fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favorable coalition’s declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. [13]

Abrasion transfer

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of material from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles however undergo a continuous change in size as long as the conditions that lead to the transfer of material exist. [13]

Manufacturing of pellets directly from powder

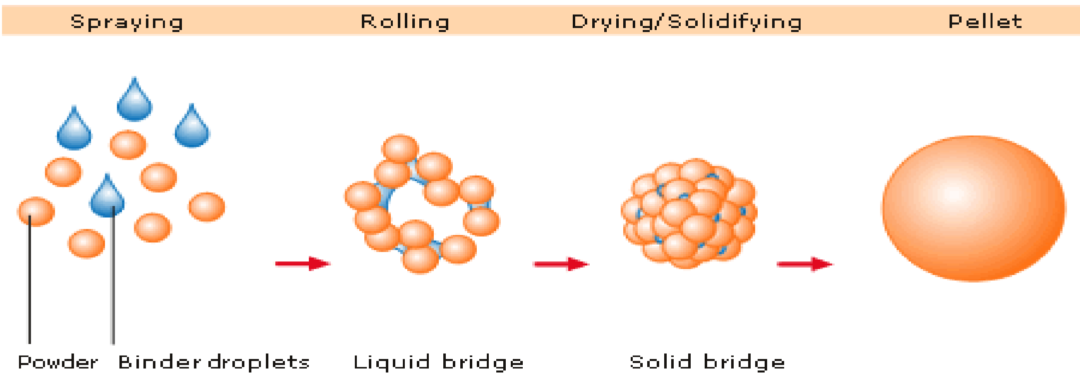


Figure No: 3

Powder is mixed and moistened with a solvent or binder and the powder bed is set into a centrifugal motion (Fluid Bed Pelletizing in the rotor). The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on density and size of the pellets. The moist pellets are subsequently dried in the fluid bed.

Lipid/Hot Melt Coating [23]:

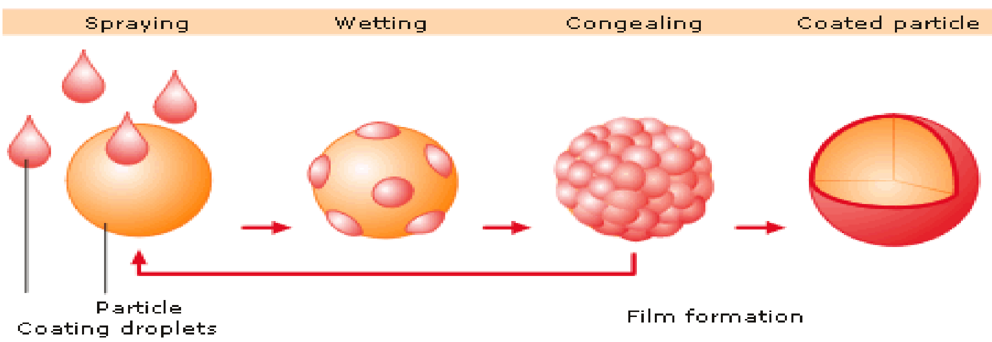


Figure No: 4

Lipid/Hot melt coating is a very effective process for the application of waxes and molten materials as protective films for manipulating the particle properties.

Glatt offers Fluid Bed Coating (Top Spray Coating, Bottom Spray and Tangential Spray) as a technical solution for coating different particles and tablets. The coating fluid is sprayed onto solid materials, which are presented to it. The introduction of process air causes the film coating to solidify and a small droplet which is low viscosity ensures that the distribution is uniform. The time and energy-intensive evaporation of solvents can be dispensed with by the use of molten materials as coating liquids.

1.5.2 PELLETIZATION TECHNIQUES

- Powder layering
- Extrusion-Spheronization
- Compression
- Solution/Suspension layering
- Globulation
- Balling or Spherical agglomeration
- Melt spheronization
- Cryopelletization

Powder layering[24,25]

Principle

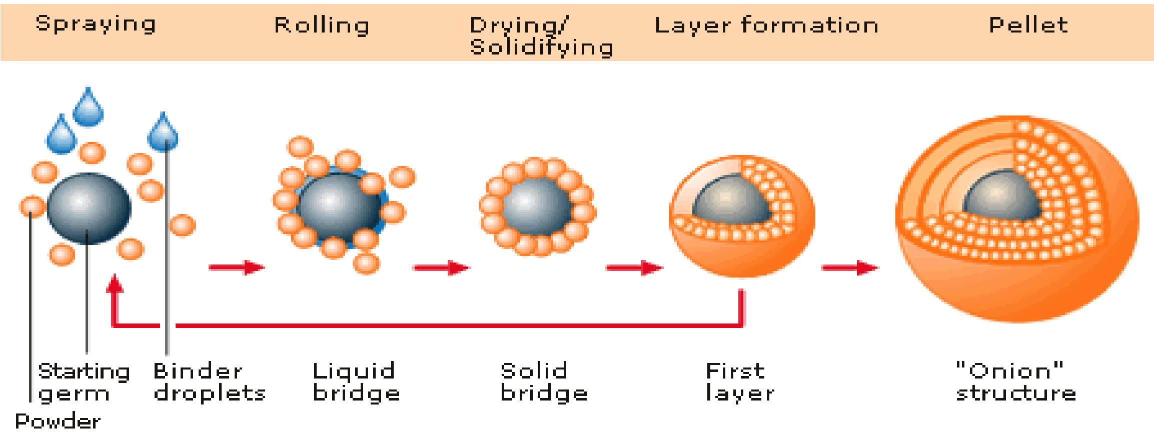


Figure No: 5

- It is carried out in Fluid bed Granulator or Tangential spray equipment.
- During powder layering, a binding solution and a finely milled powder are added simultaneously to a bed of starter seeds at a controlled rate. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid.
- These liquid bridges are eventually replaced by solid bridges derived either from a binder in the application medium or from any material, including the drug substance, that is soluble in the liquid.
- Successive layering of the drug and binder solution continues until the desired pellet size is reached. Throughout the process, it is extremely important to deliver the powder accurately at a predetermined rate and in a manner that maintains equilibrium between the binder liquid application rate and the powder delivery rate.
- If the powder delivery rate is not maintained at predetermined equilibrium levels, over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized.
- Towards the end of the layering process, it is likely that fines may be generated owing to potential interparticle and wall-to-particle friction and appears in the final product, there by lowering the yield.
- The problem can be overcome if the application medium is sprayed on cascading pellets at the end of layering process to increase the moisture level at the pellet surface and facilitate layering of the fines onto the pellets.

Extrusion-Spheronization [26,27,28]

- Extrusion–spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening.
- The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted into a plastic mass that can be easily extruded.
- The extruded strands are transferred into a spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating

friction plate and are pushed outward to the stationary wall of the processing chamber by centrifugal force.

- Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved.

Principle of the Granulate Spheronizing Process:

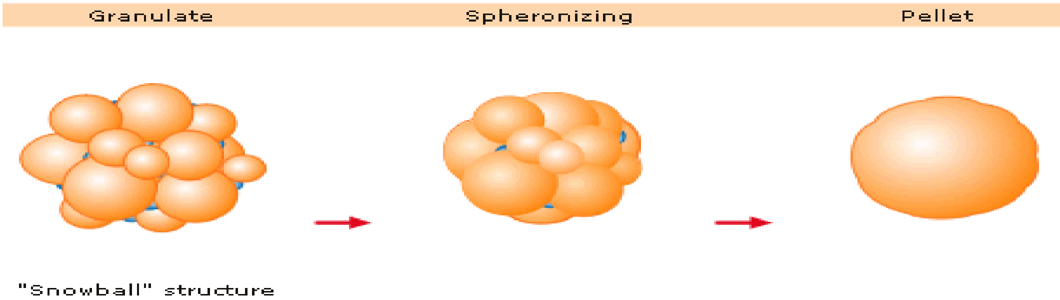


Figure No: 6

Principle of the Extruded Product Spheronizing Process:

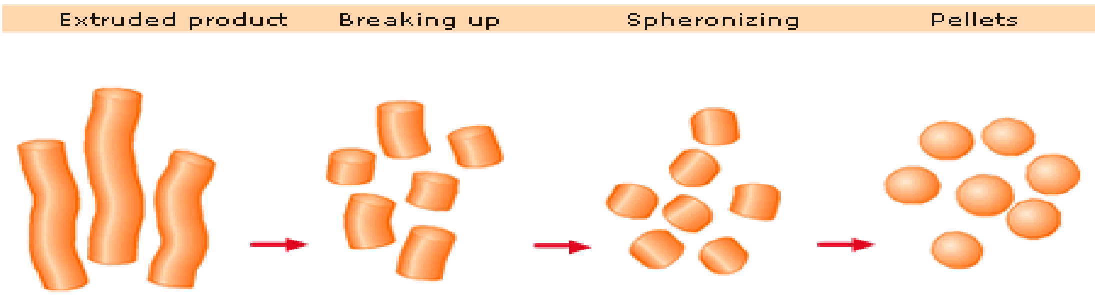


Figure No: 7

Compression:

- It is a type of Compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure.
- This process can be achieved by using extrusion-spheronization technique.

Solution/Suspension layering [29,30]:

Principle

- Layering processes involve loading solid inert cores with drugs and/or excipients. Inert cores are placed in a suitable vessel such as a coating pan or a fluid bed and are layered according to different methods.

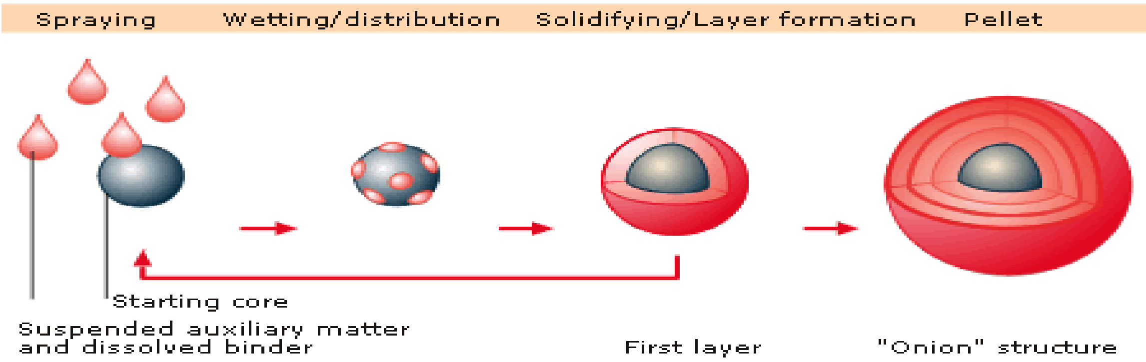


Figure No: 8

- Some methods consist of spraying onto the cores a solution/suspension containing both drug and binding agent. Others are based on layering the drug directly in powder form where drug loading occurs by gravity and adhesion is ensured by a liquid binder sprayed onto the cores.
- The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery.
- In the case of spherical inert cores such as non-pareils, the layering techniques from solution/suspensions produce homogeneous drug loaded particles, which retain an approximately spherical shape.

Fluidized bed Coater:

Principle:

Fluidized bed coating is a process that takes place inside a fluidized bed where by a coat is introduced to cover the intended object in order to protect or modify its behavior. Particulate coating is a form of fluidized bed coating involving the coating of solid particles inside the bed. In the process, a layer is deposited onto the surface of fluidized solid particles by spraying with a solution of the coating material. The fluidizing gas is also used to dry the deposited solution to form a coat on the surface of the particle. Fluidized beds are used for coating because of their high energy and mass transfer. Fluidized beds for film coating can be divided into three groups.

Types:

- Top spray
- Tangential (Rotating disk granulator)
- Bottom spray (Wurster Process)

Fluid Bed Coating Flow Chart:

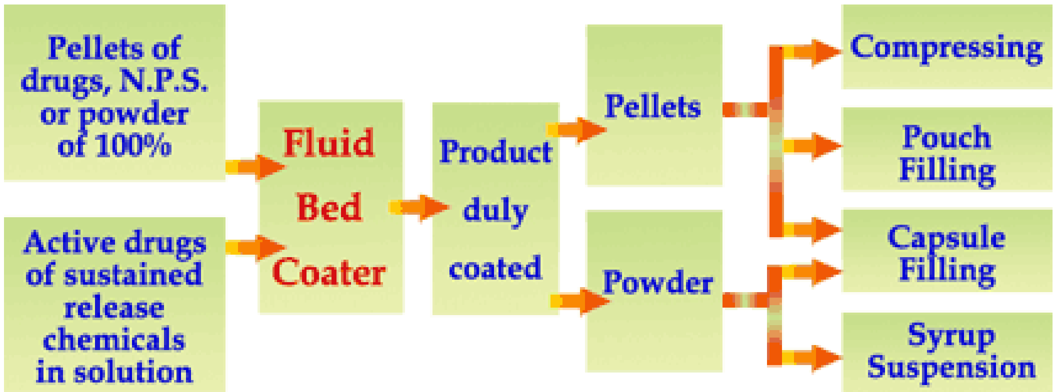


Figure No: 9

Top spray:

- This process is used for general coatings right up to enteric coating.
- With top spray coating in the fluid bed, particles are fluidized in the flow of heated air, which is introduced into the product container *via* a base plate.
- The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow.
- The expansion chamber is lengthened to allow powder to remain fluidized longer and to move with a higher velocity, so that agglomeration is minimized. The expansion chamber is conically shaped to allow uniform declaration of air stream. The filter housing is larger and designed to shake the fines back into the bed interrupting fluidization; this reduces agglomeration tendencies.
- The nozzle is positioned low in the expansion chamber so that coating material impinge on the fluidized particle a short distance from the nozzle, this reduces droplet spray drying and provides for longer subsequent drying of the coated particles.

Tangential spray:

- Ideal for coatings with high solid content.
- These techniques have been extended for coating operations and combined with an expansion chamber to form the rotating disk granulator and coater fluid bed device. The basic design employs a rotating disk in the product container.
- The disk can be moved up or down to create a variable slit opening between the outer perimeter of the disk and the sidewall of the container. Air is drawn into the product container through the slit under negative pressure.
- This fluidizes the material along the circumferential surface of the product container. At the same time the disk rotates at varying speeds and moves the product by centrifugal force to outer portions where it is lifted by fluidizing air stream into the expansion chamber.
- As the material decelerates, it descends to center of the disk and repeats the same sequence.
- The fluidization pattern is often described as a spiraling helix or rope-like pattern around the inside of rotor chamber. Spray nozzles can be immersed in the bed of fluidized material and spray applied in tangential fashion with respect to the particle flow.
- Very thick film layers can be applied by means of the rotor method.

Bottom spray:

- This process is particularly suitable for a controlled release of active ingredients. In the Wurster process, a complete sealing of the surface can be achieved with a low usage of coating substance.
- Inside the container a second cylinder (coating partition) which is raised slightly above the perforated plate, centered. Below this partition a spray nozzle used to dispense the coating solution is fitted in the base plate resulting in a spray pattern that is concurrent with the air feed.
- The perforated plate is designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter.

- The design allows the substrate particles to be pneumatically transported upward through the coating partition and downward outside this partition.
- By using a wurster cylinder and a base plate with different perforations, the particles to be coated are accelerated inside the wurster tube and fed through the spray cone concurrently.
- As the particles continue travelling upwards, they dry and fall outside the wurster tube back towards the base plate. They are guided from the outside back to the inside of the tube where they are once again accelerated by the airflow. This produces an extremely even film coating. Particles of different sizes are evenly coated.

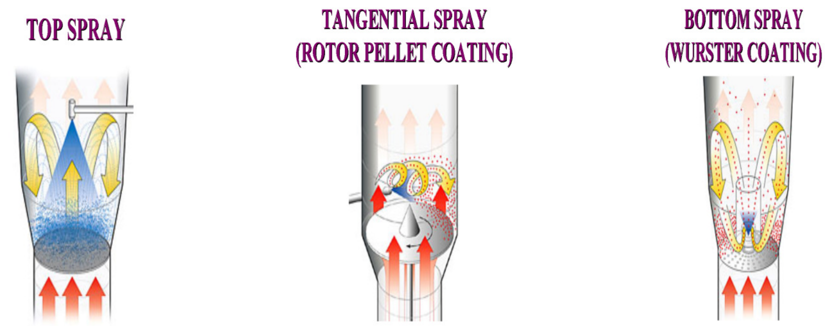


Figure No: 10

Globulation

- **Spray drying** is the process in which drugs in the form of suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs. [31]
- **Spray congealing** is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids and is sprayed in to an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables. [32]

Balling or Spherical agglomeration

- It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures.
- The process consists of conversion of finely divided particles in to spherical particles upon the addition of appropriate amounts of liquid.

Liquid induced

- Liquid is added to the powder before or during the agitation step. As powders come in contact with a liquid phase, they form agglomerates or nuclei, which initially are bound together by liquid bridges.
- These are subsequently replaced by solid bridges, which are derived from the hardening binder or any other dissolved material within the liquid phase. The nuclei formed collide with other adjacent nuclei and coalesce to form larger nuclei or pellets.

Melt induced

- It is similar to liquid-induced processes except that the binding material is a melt. Therefore, the pellets are formed with the help of congealed material without having to go through the formation of solvent-based liquid bridges. [33,34]

Tumbling melt granulation

- A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator.
- The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads.
- In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value.
- The particle size of a meltable material should be 1/6 or lower than the diameter of the seeds. High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity. [35,36]

Cryopelletization

- Cryopelletization is a process whereby droplets of a liquid formulation are converted into solid spherical particles or pellets by using liquid nitrogen as the fixing medium.
- The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and liquid nitrogen. The pellets are dried in conventional freeze dryers. [37,38]

2. LITERATURE REVIEW

Kotta Kranthi Kumar *et al.*, designed and evaluated multi particulate system of extended release indomethacin capsules USP. By pellatization method: The indometahcin is coated on inert sugar spheres by using povidoneK-30 as a binder solutions and Hydroxypropyl methylcellose, Ethyl cellose coating agents used for extended release action. The prepared capsules were evaluated for content uniformity weight variation, in-vitro disintegration time, assay, and in-vitro drug release study. All the formulation exhibited assay, content uniformity with in the range given in USP[39].

S. Eskandari *et al.*, developed an extended release pellet formulation of indomethacin by the centrifugation (rotary fluid bed granulation) or powder layering method. Layered, nonpareil pellets composed of sugar, Avicel PH 101 and lactose by using FREUND CF granulator and were treated by a binder solution (HPC-L) applied by spray gun. The amount of Eudragit NE 30 D, Opadray and SDS in coating solution adjusts release of the pellets. It would be possible to maintain a constant anti-inflammatory serum concentration of indomethacin by ingestion of only one unit dose every 12 hours, and reduce the gastrointestinal disturbances [40].

Kar S K *et al.*, reported controlled release preparations to reduce the gastro irritant and ulcerogenic effects of non-steroidal anti-inflammatory drugs. A develop matrix tablet-based controlled release formulations of Indomethacin, using ethyl cellulose as the rate-controlling polymer. In order to prevent initial release of the drug in the acidic environment of the stomach, cellulose acetate phthalate was incorporated in the matrix in varying amounts. The combination of cellulose acetate phthalate with ethyl cellulose in the matrix base can be an effective means of developing a controlled release formulation of indomethacin with very low initial release followed with controlled release up to 14-16 hours [41].

P.A. Elchidana *et al.*, developed Indomethacin extended release formulation by pelletization using the method of extrusion/ spheronization. The drug containing pellets were further coated to achieve the required release profile as per USP. Coating systems developed on the principle of microporous membrane drug delivery using soluble salt gave the best results [42].

Mircea hirjau *et al*., produced and characterized pellets containing a non steroidal anti-inflamatory (NSAID) drug, coated with an entric polymer by extrusion-spheronization using microcrystalline cellulose (Avicel PH 101) as a spheronization aid, polyvynilpyrrolidone K30 as a binder and lactose as filler. The pellets were analysed for the following physical parameters, relevant for subsequent processing of the pellets:size distribution, circularity, bulk density. The pellets have shown characteristics suitable for hard capsule filling [43].

A. Akhgari *et al*., evaluated the effect of two factors (ratio of Eudaragit S100 and Eudaragit L100 and the coating level) on indomethacin release from pellets. Coating formulations were designed on the full factorial design. In the ratio of Eudaragit S100: Eudaragit L100 (1:4, 1:1 and 1:0) and the level of coating (10%, 15%, 20% w/w) respectively. Polymers were coated onto the pellets containing 20% (w/w) indomethacin, using a fludized bed coating apparatus. Dissolution test was carried out in media with different pH (1.2, 6.5, 6.8 and 7.2). The dissolution data revealed that the level of coating and the ratio of polymers are very important to achieve optimum formulation [44].

M. A. Hull *et al*., suggested the non-steroidal anti-inflammatory drug indomethacin has anti-colorectal cancer activity. Although indomethacin itself has significant adverse effects, including serious upper gastrointestinal toxicity, the development of novel derivatives that may have an improved safety profile means that further investigation of the anti-colorectal cancer activity of indomethacin is warranted [45].

Shun Por Li et al., prepared indomethacin pellets by spraying slurry of indomethacin, EudragitB 5-100, dibutyl sebacate and alcohol onto an appropriate mesh fraction of nonpareil seeds using appropriate processing equipment. The average particle diameter and the overall particle size distribution of the indornethacin powder were found to be critical factors influencing the physical properties of the pellets. Micronized indomethacin powder, having an average particle diameter of four microns and a particle size distribution ranging from one to thirteen microns, was found to be the optimum for this layering process. The layering process was found to greatly affect the release characteristics of the drug from the beadlets [46].

Shan-Yang Lin *et al*., estimated the influence of ethyl cellulose (EC) with different viscosity grades on *in vitro* drug release from EC matrix tablets containing Indomethacin. Four viscosity grades of EC (7, 10, 50 and 100 cp) were used. The drug release from Indomethacin tablets marginally increased with an increase in viscosity grade. The viscosity grade effect on release rates would be differences in tablet porosity [47].

A. Mesnukul *et al*., studied the carrier system could effectively enhance the solubility of indomethacin and an addition of xanthan gum could sustain the drug release. Eudragit L100 film coating could protect the carrier not to be disturbed with HCL buffer pH 1.2 and could dissolve in phosphate buffer pH 6.2, therefore, the drug release from coated tablet was initially very low but subsequently gradually released and prolonged in phosphate buffer pH 6.2[48].

H. Lippold *et al*., developed guaiphenesin pellets are coated in a fluidized bed with aqueous ethyl cellulose dispersions (Aquacoat ECD-30) containing different amounts of dibutyl sebacate (DBS) as plasticizer. Optimal film formation and zero-order release rates are obtained if the produced microcapsules (MC) are treated with heat about 10°C above the minimum film forming temperature (MFT). At 25ºC of the release medium the coats of the MC with a MFT of 40-50ºC are in the glassy state, thus the permeability is extremely low [49].

Andrei Dashevsky *et al.*, prepared a rupturable, capsule-based pulsatile drug delivery system with pH-independent properties by using aqueous coating. The drug release is induced by rupturing of the top-coating, resulting by expanding of swellable layer upon water penetration through the top-coating. A higher coating level was required, when aqueous dispersion was used, compared to organic coatings. However, an advantageous aspect of the aqueous coating was the lower sensitivity of the lag time to a deviation in the coating level [50].

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P. B. Deasy *et al*., developed two new pelletized formulations of indomethacin and compared against pellets from the proprietary product, Indocid-R. Extensive dissolution testing involving pH-shift and topographical profiling showed that the new product containing polyvinyl pyrrolidone had slightly faster in vitro release than the commercial product, but the other new product containing sodium lauryl sulphate had reduced drug release. However, on *in vivo* testing in dogs, the new product containing sodium lauryl sulphate had the highest bioavailability of the three preparations examined due to its effect as a penetration enhancer [51].

Mundada .AS *et al.*, investigated for sustaining the drug release from pellet by using Diclofenac sodium (10% w/w) as a model drug by extrusion and speronization. The drug containing pellets were coated using DB plasticized film-coating solutions. Films prepared from novel biomaterial with 20% and 30% w/w plasticizer concentration [52].

Nantharat Pearnchob *et al.*, studied the film forming ability of ethylcellulose powder and the effect of formulation factors (plasticizer type and concentration) and curing conditions (curing temperature and time). Although ethylcellulose-coated pellets had an uneven surface, extended drug release could be obtained with coating level of 15%. Because of its high glass transition temperature, ethylcellulose-coated pellets showed unchanged drug release profiles upon storage at room temperature for 3 years [53].

M. Anand Kumar *et al*., formulated Tamsulosin Hcl extended release pellets using a combination of ethyl cellulose N-50 and Eudragit L-100 as a coating material. Initially trials were done to optimize the drug loading on to sugar pellets for its uniformity of size and Assay, varying the concentration of HPMC E-5 as binder, Aerosil as lubricant and sodium starch glycollate as disintegrant. The release study at 2, 3, 5 and 8 hours were the target responses and were restricted to 13-34%, 47-68%, NLT 70%, NLT 80% respectively. The optimal coating formulation was achieved with Eudragit L-100 9% of the weight of the drug loaded pellets and ethyl cellulose N-50 with 25% of the Eudragit L-100 content. The drug release from the optimized pellets was compared with the Innovator product FLOMAX capsule showed the similarity factor (F2) of 76.43[54].

KHAN M. S *et al.*, prepard and evaluated microporous pellets loaded with Indapamide (IP) using blend of Avicel PH 101 (Microcrystalline cellulose) and sodium chloride (Nacl) by extrusion/ spheronization technique for controlled release. Solid, discrete, reproducible pellets were obtained. Sieve analysis data indicated that the size of prepared pellets were in the range of 1135µm to 1245µm. Prepared pellets were spherical in shape, have dent surfaces with pores on the surface, as evidenced by scanning electron microscopy (SEM). The optimized formulation F3 showed 91.41 % drug release up to 24 hours. The stability studies showed no significant difference in drug content. The drug release performance was greatly affected by the polymer and pore forming agent used in preparation of pellets [55].

Nisar-Ur-Rahman *et al*., developed controlled release diltiazem pellets with Eudrgit NE40 and the effects of percent drug layering, pH and stirring speed of dissolution media on drug release were also evaluated. The release profile of coated pellets was found to be inversely proportional to the thickness of the polymer coat and desirable controlled release characteristics could be achieved by manipulating the coating levels. The percent drug layering onto inert pellets had no effect on the release rate of coated pellets. Moreover, diltiazem HCL release was fairly independent of pH [56].

S. Muschert *et al*., to elucidated the drug release mechanisms in pellets coated with aqueous ethyl cellulose dispersion, providing long term stable drug release profiles and containing different types of starter cores. DiltiazemHCl release from pellets coated with ethyl cellulose containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer is primarily controlled by drug diffusion through the intact polymeric membranes[57].

Mustafa Sinan Kaynak *et al*., formulated of controlled release Glipizide incorporated into non-pareil seeds by spraying glipizide in a solution in methylene chloride containing polyvinyl pyrolidone (PVP 30K) as a binder and talc as anti sticking agent Upper layer coating was Eudragit RS 100 PM and Eudragit RL 100 PM polymers were used which provide the release of the active ingredients independent of pH of the environment. The amount of the coating solution is inreased, the release of glipizide was significantly prolonged. The dissolution profiles of the manufactured pellets were evaluated in pH 7.4 phosphate buffer solution in USP apparatus [58].

Rakhee A. Surana *et al*., formulated Phenyl propanolamine hydrochloride sustained release pellets. Uni Glatt fluid bed processor (Glatt, Germany) was used for drug solution layering and also for sustained release coating. By using hypromellose E5, ethylcellulose 10cps and ethylcellulose 45cps polymers in combination. Polymeric solution was prepared by dissolving polymers into different solvents in different proportion to form clear coating solution. The pellets were evaluated for appearance, shape and size analysis, density, assay, content uniformity, in-vitro drug release studies, stability study and kinetic study. The optimized batches were charged for stability at 40°C and 75% RH for 2 months. The drug release studies were repeated after storage for 2 months at conditions like room temperature (RT) and 40ºC and 75% RH [59].

N. A. Muhammad *et al*., studied the release of a water soluble drug in various dissolution media from pellets coated with HPMCP 50 with 30% plasticizer containing various levels of hydroxyl propylcellulose (HPC) or HydroxyPropyl-MethylCellulose (HPMC), HPMCP 50 alone without a plasticizer does not form a film. Drug release from coated pellets was found to be II50. Drug release was increased as the percentage of HPC was increased. Higher release rates were obtained with HPMC compared to HPC. Coating level significantly influenced drug release in 0.06 N HCL; however, less of an effect was observed at pH 5.5 [60].

P. K. Lakshmi *et al*., formulated Duloxetine hydrochloride enteric coated pellets using fluidized bed. Three separate layers, the drug layer, the barrier layer and the enteric layer were coated onto the inert core pellets. Various other properties such as surface morphology, bulk and tapped density, hausner´s ratio, yield of pellets, moisture content and particle size distribution were also studied in the optimized pellets [61].

D. Yadav *et al*., developed and evaluated time dependent rupturable multiparticulate pulsatile delivery system for glipizide. Microcrystalline cellulose (MCC) based pellets containing glipizied were prepared by extrusion-spheronization technique (Type 1 pellets) coated with two consecutive layers, a swellable layer of hydroxyl-propylmethyl cellulose (HPMC) and a rupturable layer of plasticized ethylcellulose (EC) with fluidized bed coating. Drug release and water uptake studies were carried out on formulated pellets [62].

A. Kramar *et al*., evaluated three formulation parameters for the application of polymethacrylic films from aqueous dispersions in order to obtain multiparticulate sustained release of diclofenac sodium. In this film coating of pellet cores was performed in a laboratory fluid bed apparatus. To influenced on plasticizer concentration on the drug release from the pellets [63].

S. K. Singh *et al*., developed delayed release micropellet dosage form for Lansoprazole. Drug-Excipient compatibility data and prototype formulations, the formula that found to be giving the desired drug release pattern was considered as the optimized formulation showed delayed release profile and it was within the USP limits, and also this formulation done by FBC process which is a sophisticated method[64].

M. Korber *et al*., evaluated strategies to set-off the very strong pH-dependent solubility (solubility: 80 mg/ml at pH 2 and 0.02 mg/ml at pH 7.5, factor 4000) of a mesylate salt of weakly basic model drug (pKa 6.5), in order to obtain pH-independent extended drug release. The incorporation of an enteric polymer layer underneath the EC/HPC coating decreased the free base formation at pH 7.5 and thus resulted in a more complete release of up to 90% of the drug loading over 18 hours. The release enhancing effect was attributed to an extended acidification through the enteric polymer layer [65].

F. Siepmann *et al*., used blends of aqueous dispersions of a water-insoluble and an enteric polymer, namely ethylcellulose : hydroxypropyl methylcellulose acetate succinate (EC:HPMCAS) and ethyl cellulose:methacrylic acid ethyl acrylate copolymer (EC:EudragitRL), as coating materials to control theophylline release from matrix pellets. Varying the polymer blend ratio, broad ranges of drug release patterns were obtained at low as well as at high pH. The release profiles were rather similar for both types of blends in 0.1 M HCl, where as significant differences were observed in phosphate buffer pH 7.4 and the drug release at high pH was much slower for EC:HPMCAS blends compared to EC:EudragitRL blends, although HPMCAS leached out more rapidly (and to a higher extent) from the film coatings than EudragitRL. The EC structures remaining upon HPMCAS leaching are mechanically stronger and drug release is controlled by diffusion through the polymeric remnants[66].

G.J. Vergote *et al*., developed controlled release pellet formulation using a nanocrystal colloidal dispersion of ketoprofen process the aqueous nanocrystal colloidal dispersion into a hydrophobic solid dosage form a spray drying procedure was used. The in vitro dissolution profiles of wax based pellets loaded with nanocrystalline ketoprofen are compared with the profiles of wax based pellets loaded with microcrystalline ketoprofen and of a commercial sustained release ketoprofen formulation. The surfactants used to increase the dissolution rate were either added during the production process of the nanocrystal colloidal dispersion (sodium laurylsulphate) or during the pellet manufacturing process (Cremophor RH40) [67].

J. J. Sousa *et al*., studied the different ways in which water can be considered an active excipient in terms of the amount used to obtain the wet mass, the dispersion within the mass and the drying process. Physical characteristics of the pellets were analyzed for pellets within the same fraction size of 1-1.4 mm diameter. The analysis indicated that the amount of water and the extrusion and drying processes are of great importance and influenced the physical characteristics of the resultant pellets. Hence, water should be considered as an 'active' excipient rather than an inert component of the extrusion masses [68].

S. Muschert *et al*., studied the drug release mechanisms from aqueous ethylcellulose-coated pellets containing different types of drugs and starter cores. Theophylline, paracetamol, metoprolol succinate, diltiazem HCL and metoprolol tartrate were used as model drugs exhibiting significantly different solubilities (e.g. 14, 19, 284, 662 and 800 mg/ml at 37 °C in 0.1 N HCL). Drug release was found to be controlled by diffusion through the intact polymeric membranes, irrespective of the drug solubility and type of core formulation. The ethylcellulose coating was dominant for the control of drug release, minimizing potential effects of the type of pellet core and nature of the surrounding bulk fluid, e.g. osmolality. Thus, this type of controlled drug delivery system can be used for very different drugs and is robust [69].

N. Vyas *et al*., to developed ER formulations of a practically insoluble macrolide antibiotics clarithromycin suitable for once-a-day oral administration. The polymers carbopol 71G, low-viscosity (LV) hypromellose, polyox 750N, hypromellose K4M as well as LV-ethylcellulose (EC) interspersed with pore-formers like Klucel LF and LV hypromellose. The formulation comprised of drug granulated and tableted with commonly employed tableting aids like MCC, talc, lactose, colloidal silicon dioxide and magnesium stearate [70].

Sandhiya. K. M *et al*., formulated the oral sustained release matrix tablets of Ambroxol HCl in order to improve efficacy, reduce the frequency of administration and better patient compliance. Differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. Matrix tablets of Ambroxol Hydrochloride were formulated employing hydrophilic polymers HPMC K100M, Carbopol 934P and hydrophobic polymer Ethyl cellulose as release retardant polymers. Matrix tablet containing Ethyl cellulose (F7) formulation were found to show good initial release 24.24% at 2 hrs and at the end of 12 hrs the drug release was found to be 96.86%. The n value for F7 obtained from Korsmeyer-peppas model confirmed that the drug release was anomalous diffusion mechanism [71].

Siddaramaiahb *et al*., developed Theophylline by the pelletization technique using the extrusion/spheronization method. The drug-containing pellets were further coated to achieve the required release profile. The different polymeric coatings of ethyl cellulose (EC), hydroxy propyl methyl cellulose (HPMC) and Eudragit S-100 were used. From that coated pellets were characterized with regard to the percentage yield, density, friability, sphericity, drug entrapment efficiency and size distribution. Coated drug pellets were further characterized by Fourier transform infrared (FTIR) spectroscopy. Drug release profiles were studied for uncoated pellets, pellets coated with plain polymer and pellets coated with polymeric containing the pore-forming agent, SLS. The *in vitro* drug release revealed that formulation B4 had the expected release profile (24 hrs releases). The optimized formulation is an ideal formulation for once-a-day administration [72].

George Reyes *et al*., investigated the application of an aqueous ethylcellulose dispersion (Surelease) as a wet granulation agent (release retardant binder), on the release of theophylline from extended release (ER) inert matrix tablets. The influence of varying polymer concentration, filler choice and compression force on drug release profiles were studied [73].

H. Kranz *et al*., identified an efficient tool to adjust drug release patterns from aqueous and organic ethylcellulose (a gastrointestinal insoluble polymer) coated pellets and to evaluate the long term stability of the film coatings. The drug release rates from organic coated ethylcellulose : Kollicoat MAE 100 P pellets stored at ambient and stress conditions did not change which could be explained by differences in the film formation process. The addition of methacrylic acid/ethyl acrylate copolymer to ethylcellulose film coatings in combination with an organic coating process is able to achieve broad ranges of drug release patterns and to overcome storage instability [74].

Raghavendra rao N. G *et al.*, developed of rapidly disintegrating oral tablets by direct compression using co-grinding and solid dispersion methods by using chlorthalidone as a model drug. The solid dispersions and co-grinding method were followed to increase solubility and bioavailability. The tablet formulation containing polyvinyl pyrrolidone K-12 solid dispersion showed maximum drug release than the chlorthalidone polyvinyl pyrrolidone K-12 co-grinding method. Solid dispersion of the drug with the hydrophilic carrier poly vinyl pyrrolidone can enhance the dissolution rate of chlorthalidone tablets [75].

P. Subhash Chandra Bose *et al.*, prepared floating tablets of diltiazem HCl using xanthan gum as carrier by direct compression technique using PVP K-30 as a binder and sodium bicarbonate for development of CO_2 [76].

Fars K. Alanazi *et al.*, prepared albendazole microparticles with hydrophilic polymers such ashydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) using spray drying technique. The highest dissolution of ABZ was obtained with HPMC in 1:1 ratio and with both PVA and PVP in ratio of 1: 4 microparticles. The transformation of ABZ from crystalline to amorphous state by spray drying and the hydrophilic coating of drug particles by the polymers are considered among the factors which contributed in improvement of ABZ dissolution[77].

Chowdary K. P. R *et al.*, evaluated starch phosphate a new modified starch, PVP K-30 and PEG 4000 as carriers in solid dispersions for enhancing the dissolution rate and efficiency of etoricoxib, a BCS class II drug. Hence addition of PVP and PEG 4000 to the solid dispersions in starch phosphate is recommended to enhance the dissolution rate of etoricoxib, a BCS class II drug [78].

G. Ashwini Kumar et al., developed a modified release capsules of mebeverine hydrochloride which are designed to controlled release action. Modified release capsules of mebeverine hydrochloride were formulated by using the pelletization process by drug layering on inert sugar pellets by using PVPK-30 as binder. The drug layered pellets were coated by using the Eudragit L-100 and P.E.G-6000 as a first coating material by using I.P.A and water as solvents. The coated pellets were again coated by using the Ethyl cellulose N-50, P.E.G-6000, I.P.A and water as coating material to sustain the drug release. The coated pellets size and shape is observed during processing. The coated pellets is filled in capsules No.2 and these capsules was evaluated for assay, weight variation, content uniformity, lock length, moisture content, disintegration and in-vitro dissolution tests and these was with in the range. There is no physicochemical interaction between drug and excipients and the compatibility study is carried out for four weeks at different temperature conditions. The coating step is divided into two steps for getting the desired release rate [79].

3. AIM OF WORK

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain and inflammation caused by condition such as osteoarthritis, gout, ulcerative colitis, colon cancer. Its biological half-life is 4.5 hrs.

When given conventionally it gets released in the upper GIT there by causing irritation and ulcer in the upper GIT. The dosage form should be designed in such a way that it should minimize or prevent drug release in the acidic environment of upper GIT and start releasing the drug in a controlled manner once it reaches the alkaline environment of small intestine.

Aim of the present work is to formulate the indomethacin pellets to present it in the form of capsules (Extended release pellets).To develop and over an extended period of time in the gastro intestinal track and compared the in-vitro dissolution profile with that of the marketed product.

OBJECTIVES:

- Reduced frequency of dosage form
- Improved patient compliance
- Maximizing bio availability with a minimum dose
- To study the release profile of the formulation using various polymer

4. PLAN OF WORK

The present approach was made to formulate the Indomethacin extended release pellets and evaluation.

The stages involved in the plan of work are as follows:

1. Preformulation studies of drug

a. Raw material analysis of indomethacin

b. Drug-Excipient compatibility study

c. Physical observation

d. Construction of calibration curve by UV spectrophotometer

e. FTIR study

f. Particle size analysis

2. Formulation of extended release pellets

- Drug layering
- Extended release coating

3. Evaluation of pellets

- Bulk density
- Tap density
- Compressibility index (Carr's index)
- Hausner ratio
- Content uniformity
- Weight variation
- Percentage yield
- Capsule lock length
- LOD (Loss on drying) of the pellets
- In vitro drug release
- Investigation of drug release kinetics
- Comparative in vitro drug release studies with market sample
- Stability study for selected formulation

5. LIST OF MATERIALS AND EQUIPMENTS

Table No.1: List of materials used

S. NO	MATERIALS	NAME OF THE COMPANY
1	Indomethacin	Fabbrica Italiana Sintetici, Italy.
2	Ethyl cellulose (4cps)	Colorcone Asia Ltd, Mumbai.
3	Sodium lauryl sulfate	Cognis, Germany.
4	Hydroxy propyl cellulose	Hercules, China.
5	Povidone-K30	Zhangzhou Huafu Chemicals co.,Ltd. China.
6	Low substituted Hydroxy propyl Cellulose	Herculus, China.
7	Talc	Luzenac Val Chisone, Italy.
8	Sugar spheres(500-600µm)	Wemer-GmbH.co.KG, Germany.
9	Isopropyl alcohol	Merck (HPLC grade), Mumbai.
10	Empty Hard Gelatin Capsule Shell	Associated capsules Pvt.Ltd., Mumbai.

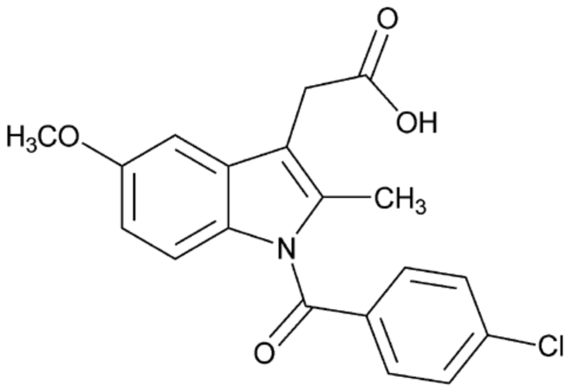
Table No.2: List of equipments used

S.NO	MATERIALS	NAME OF THE COMPANY
1	Glatt particle coater granulator(GPCG1.1)	Pam glatt, Mumbai.
2	Dissolution test apparatus	Electrolab, Mumbai, India.
3	Single pan electronic digital Balance	Mettler Toledo, Switzerland.
4	Tap density apparatus	Electrolab ETD-1020, Mumbai, India.
5	Sieves	Gotsons.
6	pH meter	Mettler Toledo, Switzerland.
7	UV-Visible Spectrophotometer (UV pharma spec 1700)	Shimadzu-corporation, U.S.A.
8	Vernier calipers	Mitutoyo corp. Japan.
9	Mechanical stirrer	REMI motors Ltd, Maharashtra.
10	Automatic capsule filling Machine	Zhejiangn Fuchang machinery co.,Ltd. China.
11	Peristalic pump	Pam glatt, Mumbai.

6. DRUG & POLYMER PROFILE

6.1 Drug Profile

Indomethacin[80,81,82,83]



Structural formula

Chemical name	1-(4-Chorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid
Molecular formula	$C_{19}H_{16}ClNO_4$
CAS No.	53-86-1
Molecular weight	357.8
Melting point	158-162°C
Functional categories	An anti-inflamatory, analgesic agent
Description	A white to yellow-tan powder
Solubility	Practically insoluble in water, soluble 1 in 50 of ethanol, 1in 30 of chloroform, and 1 in about 40 of ether, soluble in acetone
Standards	Indomethacin contains not less than 98.0 per cent and not more than 101.0 per cent of $C_{19}H_{16}ClNO_4$, calculated with reference to the dried substances
Storage	Store in well-closed, light-resistant containers

Indication:-

Clinical indications for indomethacin include

- Rheumatoid arthritis
- Ankylosing arthritis
- Arthritic gout
- Osteoarthritis
- Juvenile arthritis
- Psoriatic arthritis
- Reactive arthritis
- Colonic cancer
- Inflammatory bowel disease

Mechanism of action:

Indomethacin is a non-selective inhibitor of cyclo-oxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. Prostaglandins are hormone-like molecules normally found in the body, where they have a wide variety of effects, some of which lead to pain, fever, and inflammation. Prostaglandins also cause uterine contractions in pregnant women. Indomethacin is an effective tocolytic agent, able to delay premature labour by reducing uterine contractions through inhibition of PG synthesis in the uterus and possibly through calcium channel blockade.

Indomethacin has two additional modes of actions with clinical importance:

- It inhibits motility of polymorphonuclear leukocytes, similar to colchicines
- It uncouples oxidative phosphorylation in cartilaginous mitochondria, like salicylates

These additional effects account as well for the analgesic and anti-inflammatory properties.

Pharmacokinetics

Indomethacin is rapidly and almost completely absorbed from the gastrointestinal tract after oral ingestion. The peak concentration in plasma is attained with in 2 hrs in the fasting subject but may be somewhat delayed when the drug is taken after meals. The concentration in plasma required for an anti-inflammatory effect have not been definitely determined but probably less than 1µg/ml. Indomethacin is 90% bound to plasma proteins and also extensively bound to tissues.

Indomethacin is subject to considerable enterohepatic circulation. Metabolic reaction include O-demethylation, N-deacetylation, and glucuronic acid conjugation, the major metabolites being desmethyl Indomethacin (DMI), and desmethyldeschlorbenzoy Indomethacin (DMBI) and their glucuronides. These substances, together with unchanged indomethacin and its glucuronide, are excreted in both the urine (up to about 60% of the dose in 48 h) and the feces (up to about 30% of the dose in 96 hrs) in variable amount. Expressed as a percentage of the dose, the average amounts excreted in the urine in 48 hrs are: unchanged Indomethacin 5 to 20% (dependent on urinary pH), Indomethacin glucuronide 6 to 26%, DMI and its glucuronide 8 to 23%, DBI and its glucuronide 4 to 20%, DMBI and its glucuronide less than 3%, in the feces the major metabolites found are DMBI (up to about 16%) and DMI (up to about 12%), with only small amont of unchanged Indomethacin and DBI.

Adverse effects

Since Indomethacin inhibits both COX-1 and COX-2, it inhibits the production of prostaglandins in the stomach and intestine which maintain the mucous lining of the gastrointestinal tract. Indomethacin, therefore, like other non-selective COX inhibitors, can cause peptic ulcers. The ulcers can result in serious bleeding and/or perforation requiring hospitalization of the patient. Indomethacin also reduces plasma rennin activity and aldosterone levels, and increases sodium and potassium retention. It also enhances the effects of vasopressin. Together these may lead to:

- Edema (swelling due to fluid retention)
- Hyperkalemia (high potassium levels)
- Hypernatremia (high sodium levels)
- Hypertension (high blood pressure)

The drug may also cause elevations of serum creatinine and more serious renal damage such as acute renal failure, chronic nephritis and nephritic syndrome. These conditions also often being with edema and hyperkalemia. Additionally, indomethacin quite often causes headache (10 to 20%), sometimes with vertigo and dizziness, hearing loss, tinnitus, blurred vision (with or without retinal damage) and worsens Parkinson's disease, epilepsy, and psychiatric disorders. Cases of life-threatening shock (including angioedema, sweating, severe hypotension and tachycardia as well as acute bronchospasm), sever or lethal hepatitis and severe bone marrow damage have all been reported. Skin reactions and photosensitivity are also possible side effects.

Contraindications

- Concurrent peptic ulcer, or history of ulcer disease
- Allergy to indomethacin, aspirin, or other NSAIDS
- Patients with nasal polyps reacting with an angioedema to other NSAIDS
- Children under 2 years of age (with the exception of neonates with patent ductus arteriosus)
- Severe pre-existing renal and liver damage
- Caution: preexisting bone marrow damage (frequent blood cell counts are indicated)
- Caution: bleeding tendencies of unknown origin (indomethacin inhibits platelet aggregation)
- Caution:Parkinson´s disease, epilepsy, psychotic disorders (indomethacin may worsen these conditions)

Dose

Orally, 50 to 200 mg daily, in divided doses, with food. As suppositories 100 mg at night and in the morning if required. Maximum combined oral and rectal dose, 150 to 200 mg daily.

6.2 Polymers profile

6.2.1 Ethyl cellulose [84]

1. Non proprietary Names:

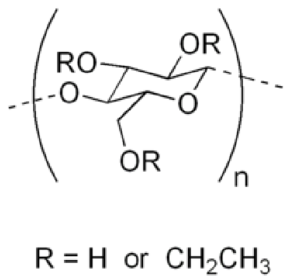
- BP :Ethyl cellulose
- USPNF : Ethyl cellulose

2. Synonyms : Ethocel, Surelease

3. Chemical name CAS Registry number: Cellulose ethyl ether [9004-57-3]

4. Empirical Formula and Molecular Weight: $C_{12}H_{23}O_6$

5. Structural formula:



6. Description: Ethyl cellulose is a tasteless free flowing white to lighten colored.

7. Application in pharmaceutical formulation and technology

The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules or pellets. Ethyl cellulose coatings are used to modify the release of a drug, or to improve the stability of a formulation. Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Drug release through ethylcellulose coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets. Ethyl cellulose may additionally be employed as a binder.

Various viscosity grades (mPa s)

Ethocel Std 4 Premium, Ethocel Std 7FP Premium, Ethocel Std 7 Premium Ethocel Std 10FP Premium, Ethocel Std 10P Premium, Ethocel Std 14 Premium, Ethocel Std 20P Premium, Ethocel Std 45P Premium, Ethocel Med 50P Premium, Ethocel Med 70P Premium, Ethocel Std 100FP Premium, Ethocel Std 100P Premium, Ethocel Std 100P, Ethocel Std 200P Premium, Ethocel Std 300P Premium.

8. Typical properties:-

- Density (bulk)**:** 0.4 g/cm3
- Moisture content**:** Ethyl cellulose absorbs very little water from humid air or during immersion, and that small amount evaporates easily.
- Glass transition temp**:**129-133°C
- Solubility**:** Practically insoluble in glycerine, propylene glycol and water
- Viscosity**:** 7 to 100 cps for 5%w/v aqueous solution at 25°C
- Melting point**:** 240-255°C

9. Stability

Stable slightly hygroscopic material chemically resistant to alkali both dilute and concentrated. Subject to oxidative degradation in the presence of sunlight or UV light at elevated temperature.

10. Incompatibility

Incompatible with paraffin wax and microcrystalline wax.

11. Safety

Non toxic, non allergic and non irritating.

6.2.2 Povidone[84]

1. Nonproprietary Names

BP: Povidone

JP: Povidone

USP: Povidone

2. Synonyms

Kollidon, Plasdone, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvinylpyrrolidone, PVP, 1-vinyl-2-pyrrolidinone polymer.

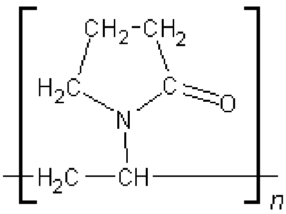
3. Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homopolymer [900l3-39-8]

4. Empirical Formula and Molecular Weight

$(C_6H_9NO)n$ 2500–3 000 000

5. Structural Formula



6. Functional Category

Disintegrant, dissolution aid, suspending agent, tablet binder.

7. Applications in Pharmaceutical Formulation or Technology

Although povidone is used in a variety of pharmaceutical formulations, it is primarily used in solid-dosage forms. In tableting, povidone solutions are used as binders in wetgranulation processes. Povidone is also added to powder blends in the dry form and granulated in situ by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. Povidone is additionally used as a suspending, stabilizing, the solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder, tablet diluent, or coating agent	0.5–5

8. Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres. Povidone K-90 and higher K-value povidone are manufactured by drum drying and occur as plates.

9 Typical Properties

Acidity/alkalinity**:** pH = 3.0–7.0 (5% w/v aqueous solution).

Melting point**:** softens at 150°C.

Moisture content**:** povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Solubility**:** freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Viscosity (dynamic)**:** the viscosity of aqueous povidone solutions depends on both the concentration and the molecular weight of the polymer employed.

10. Stability and Storage Conditions

It is stable to a short cycle of heat exposure around 110–130°C, it should be stored in an airtight container in a cool and dry place.

11. Incompatibilities

Povidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular adducts in solution with sulfathiazole, sodiumsalicylate, salicylicacid, phenobarbital, tannins.

6.2.3 Hydroxypropyl Cellulose, Low-substituted[84]

1. Nonproprietary Names

JP: Low-substituted hydroxypropylcellulose

USPNF: Low-substituted hydroxypropyl cellulose

2. Synonyms

Hyprolose, low-substituted, L-HPC.

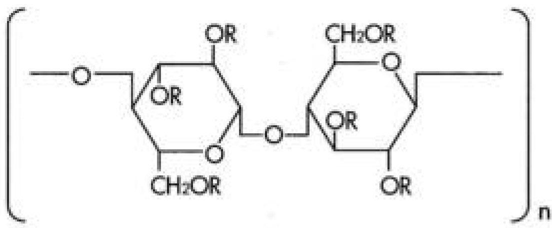
3. Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [78214-41-2]

4. Empirical Formula and Molecular Weight

R is H or $[CH_2CH(CH_3)O]mH$

5. Structural Formula



R = -H or $-CH_2CH(CH_3)OH^*$

6. Functional Categories

Tablet and capsule disintegrant, tablet binder.

7. Applications in Pharmaceutical Formulation or Technology:

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used in tableting as a disintegrant, and as a binder in wet granulation. In addition, low-substituted hydroxypropyl cellulose has been used to delay the release of drug from a tablet matrix. There are a number of grades that have different particle sizes and substitution levels. LH-11 has the medium substitution level and the largest particle size, and is typically used as an anti capping agent and disintegrant for direct compression. LH- 21 is used as a binder and disintegrant for tablets through the wet-granulation process. LH-31 is a small-particle grade used especially for extrusion to produce granules, as it has a small particle size that is better for passing a screen. The typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–25%.

8. Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odorless or has a slight, characteristic odor, and it is tasteless.

9. Typical Properties

Acidity/alkalinity**:** pH = 5.0–7.5 for 1% w/v aqueous suspension.

Melting point**:** decomposition at 275ºC.

Solubility**:** practically insoluble in ethanol (95%) and in ether, Dissolves in a solution of sodium hydroxide (1 in 10) and produces a viscous solution. Insoluble, but swells in water.

10. Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well closed container.

11. Incompatibilities

Alkaline substances may interact. If a tablet formulation contains such a material, its disintegration may be extended after storage.

12. Safety

Nontoxic and non irritant material.

6.2.4 Hydroxy propyl cellulose[84]

1. Nonproprietary Names

BP: Hydroxypropylcellulose

JP: Hydroxypropylcellulose

USPNF: Hydroxypropyl cellulose

2. Synonyms

Cellulose, Hyprolose, Klucel, Methocel, Nisso HPC.

3. Chemical Name and CAS Registry Number

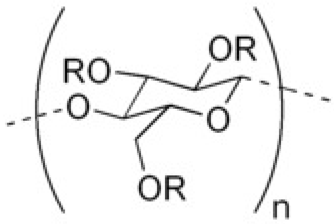
Cellulose, 2-hydroxypropyl ether [9004-64-2]

4. Empirical Formula and Molecular Weight

Molecular weight has a range of 50 000–1 250 000;

5. Structural Formula

R is H or [$CH_2CH(CH_3)O$]mH



R = H or $CH_2CH(OH)CH_3$

6. Functional Category

Coating agent, emulsifying agent, stabilizing agent, suspending agent, tablet binder, thickening agent, viscosity-increasing agent.

7. Applications in Pharmaceutical Formulation or Technology:

Hydroxypropyl cellulose is widely used in oral and topical pharmaceutical formulations; In oral products, hydroxypropyl cellulose is primarily used in tableting as a binder, film-coating, and extended-release matrix former. The release rate of a drug increases with decreasing viscosity of hydroxypropyl cellulose. The addition of an anionic surfactant similarly increases the viscosity of hydroxypropyl cellulose and hence decreases the release rate of a drug. A low-substituted hydroxypropyl cellulose is used as a tablet disintegrant, Hydroxypropyl cellulose is also used in cosmetics and in food products as an emulsifier and stabilizer.

Use	Concentration (%)
Extended release-matrix former	15–35
Tablet binder	2–6
Tablet film coating	5

8. Description

Slightly yellow-colored, odorless and tasteless powder.

9. Typical Properties

Acidity/alkalinity: pH = 5.0–8.5 for a 1%w/v aqueous solution.

Density (bulk): 0.5 g/cm3.

Melting point: softens at 130°C; chars at 260–275°C.

Moisture content: Typical equilibrium moisture content values at 25°C are 4% w/w at 50% relative humidity and 12% w/w at 84% relative humidity.

Solubility: soluble 1 in 10 parts dichloromethane,1 in 2.5 parts ethanol (95%),1 in 2 Parts methanol; 1 in 5 parts propan-2-ol,1 in 5 parts propylene glycol; and 1 in 2 parts water. Practically insoluble in aliphatic hydrocarbons, aromatic hydrocarbons, carbon tetrachloride, petroleum distillates, glycerin, and oils.

Viscosity (dynamic): a wide range of viscosity types are commercially available.

10. Stability and Storage Conditions

Hydroxypropyl cellulose powder is a stable material, although it is hygroscopic after drying. Aqueous solutions of hydroxypropyl cellulose are stable at pH 6.0–8.0.

Hydroxypropyl cellulose powder should be stored in a well closed container in a cool and dry place.

11. Incompatibilities

Incompatibility with substituted phenol derivatives, such as methylparaben and propylparaben. The presence of anionic polymers may increase the viscosity of hydroxypropyl cellulose.

12. Safety

Nontoxic and nonirritant material.

6.2.5 Sodium lauryl sulfate[84]

1. Nonproprietary Names

BP: Sodium lauryl sulfate

JP: Sodium lauryl sulfate

USPNF: Sodium lauryl sulfate

2. Synonyms

Dodecyl sodium sulfate, sodium dodecyl sulfate, sodium laurilsulfate, sodium monododecyl sulfate.

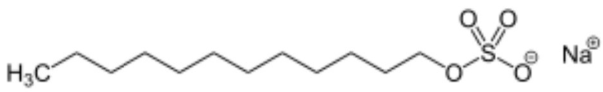
3. Chemical Name and CAS Registry Number

Sulfuric acid monododecyl ester sodium salt [151-21-3]

4. Empirical Formula and Molecular Weight

$C_{12}H_{25}NaO_4S$ Mol.wt :288.38

5. Structural Formula



6. Functional Category

Anionic surfactant, detergent, emulsifying agent, skin penetrant, tablet and capsule lubricant, wetting agent.

7. Applications in Pharmaceutical Formulation or Technology

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non parenteral pharmaceutical formulations and cosmetics. It is a detergent and wetting agent effective in both alkaline and acidic conditions.

Use Concentration (%):0.5–2.5

8. Description

Sodium lauryl sulfate consists of white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

9. Typical Properties

Acidity/alkalinity: pH = 7.0–9.5 (1% w/v aqueous solution)

Density: 1.07 g/cm^3

HLB value: 40

Melting point: 204–207°C (for pure substance)

Moisture content: 45%, sodium lauryl sulfate is not hygroscopic.

Solubility: freely soluble in water, giving an opalescent solution, practically insoluble in chloroform and ether.

10. Stability and Storage Conditions

Sodium lauryl sulfate is stable under normal storage conditions. The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

11. Incompatibilities

Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

12. Safety

It is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomac.

6.2.6 Talc[84]

1. Nonproprietary Names

BP: Purified talc

JP: Talc

USP: Talc

2. Synonyms

Altalc, Hydrous magnesium calcium silicate, Hydrous magnesium silicate.

3. Chemical Name and CAS Registry Number

Talc [14807-96-6]

4. Empirical Formula and Molecular Weight

$Mg_6(Si_2O_5)_4(OH)_4$.

5. Functional Category

Anti sticking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

6. Applications in Pharmaceutical Formulation or Technology

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations and a novel powder coating for extended-release pellets and as an adsorbent.

Uses of talc:

Use Concentration in percentage (%)

Dusting powder: 90.0–99.0

Glidant and tablet lubricant: 1.0–10.0

Tablet and capsule diluent: 5.0–30.0

7. Description

Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

8. Typical Properties

Acidity/alkalinity: pH = 7–10 for a 20% w/v aqueous dispersion.

Moisture content: talc absorbs insignificant amounts of water at 25°C and relative humidities up to about 90%.

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Specific gravity: 2.7–2.8.

9. Stability and Storage Conditions

Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

10. Incompatibilities

Incompatible with quaternary ammonium compounds.

11. Safety

Inhalation of talc causes irritation and may cause severe respiratory distress.

6.2.7 Sugar Spheres[84]

1. Nonproprietary Names

BP: Sugar spheres

USPNF: Sugar spheres

2. Synonyms

Non-pareil, non-pareil seeds, sugar seeds, Suglets.

3. Functional Category

Tablet and capsule diluent.

4. Applications in Pharmaceutical Formulation or Technology

Sugar spheres are mainly used as inert cores in capsule and tablet formulations, particularly multi particulate sustained release formulations. They form the base upon which a drug is coated, usually followed by a release-modifying polymer coating. Alternatively, a drug and matrix polymer may be coated onto the cores simultaneously. The active drug is released over an extended period either via diffusion through the polymer or through to the controlled erosion of the polymer coating. Complex drug mixtures contained within a single-dosage form may be prepared by coating the drugs onto different batches of sugar spheres with different protective polymer coatings.

5. Description

Sugar spheres as approximately spherical granules of a labeled nominal-size range with a uniform diameter and containing not less than 62.5% and not more than 91.5% of sucrose, calculated on the dried basis. The remainder is chiefly starch. The diameter of sugar spheres varies from 200 to 2000 mm.

6. Typical properties

Density: Particle size distribution: sugar spheres are of a uniform diameter. 30–35 mesh (500–600 mm)

Solubility: solubility in water varies according to the sucrose-to starch ratio. The sucrose component is freely soluble in water, whereas the starch component is practically insoluble in cold water.

7. Stability and Storage Conditions

Sugar spheres are stable when stored in a well-closed container in a cool, dry place

6.2.8 Isopropyl alcohol[84]

1. Nonproprietary Names

BP: Isopropyl alcohol

JP: Isopropanol

USP: Isopropyl alcohol

2. Synonyms

Dimethyl carbinol; IPA; isopropanol;2-propanol;sec-propyl alcohol.

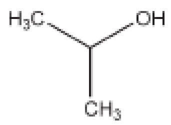
3. Chemical Name and CAS Registry Number

Propan-2-ol [67-63-0]

4. Empirical Formula and Molecular Weight

C_3H_8O Mol.wt: 60.1

5. Structural Formula



6. Functional Category

Disinfectant, solvent.

7. Applications in Pharmaceutical Formulation or Technology

Isopropyl alcohol (propan-2-ol) is used in cosmetics and pharmaceutical formulations primarily as a solvent in topical formulations. It is not recommended for oral use owing to its toxicity Isopropyl alcohol is also used as a solvent both for tablet film-coating and for tablet granulation, therapeutically, isopropyl alcohol has been investigated for the treatment of postoperative nausea or vomiting.

8. Description

Isopropyl alcohol is a clear, colorless, mobile, volatile, flammable liquid with a characteristic, spirituous odor resembling that of a mixture of ethanol and acetone; it has a slightly bitter taste.

9. Typical Properties

Boiling point: 82.48C

Flammability: flammable.

Melting point: 88.58C

Moisture content: 0.1–13% w/w.

Solubility: miscible with benzene, chloroform, ethanol (95%),ether, glycerin, and water. Soluble in acetone, insoluble in salt solutions.

10. Stability and Storage Conditions

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

11. Incompatibilities

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition.

.

12. Safety

Isopropyl alcohol is widely used in cosmetics and topical pharmaceutical formulations.

7. EXPERIMENTAL INVESTIGATION

7.1 Preparation of standard curve of Indomethacin[85]:

The drug in solution with concentration of 50 µg/ml was prepared. Serial dilutions of 5-50 µg/ml drug concentration were made by using the methanol and phosphate buffer pH 6.2. They were analyzed spectrophotometrically by measuring the absorbance at 319 nm wavelength.

(a) Preparation of pH 6.2 phosphate buffer [86]:

Potassium dihydrogen orthophosphate (KH_2PO_4) 68 gms was taken in 10 liters of purified water and 3.24 gms of sodium hydroxide pellets was mixed and adjusted to pH 6.2.

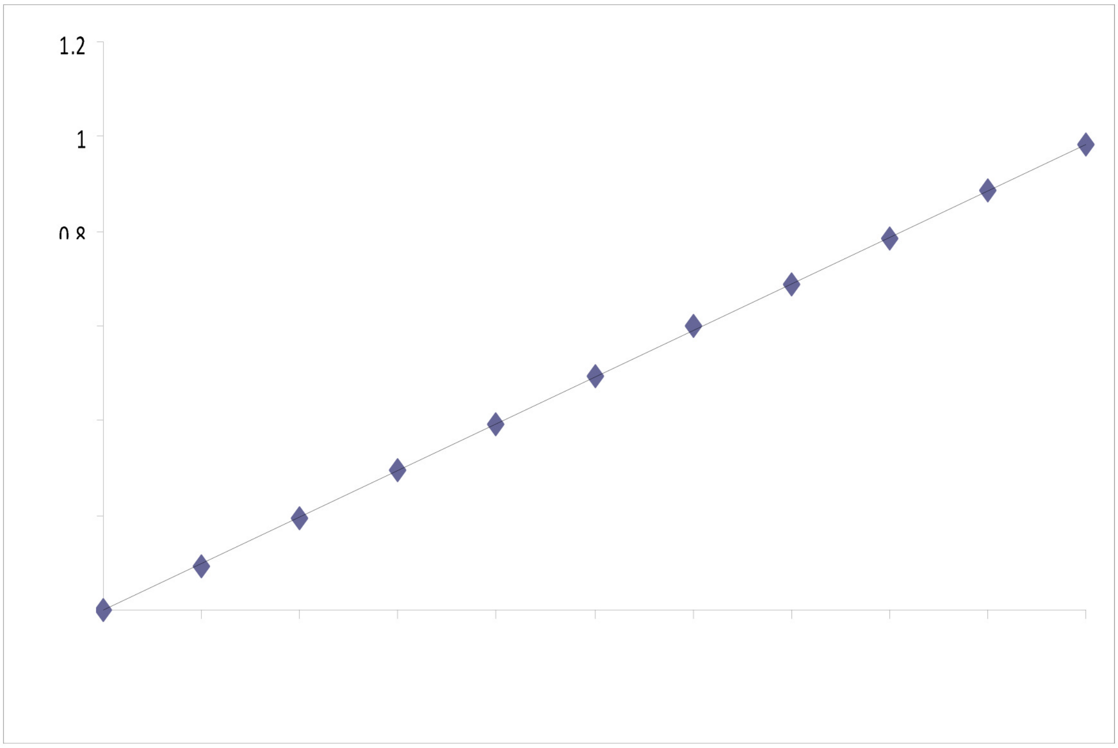
(b) Calibration curve of Indomethacin in 6.2 pH phosphate buffer:

Drug (100 mg) was dissolved in 100 ml of methanol from this solution 5 ml was withdrawn and diluted to 100 ml with phosphate buffer pH 6.2. From the stock solution serial dilution were made to obtain the solution in concentrations ranging from 5-50 µg/ml. They were analyzed spectrophotometrically by measuring the absorbance at 319 nm.

Table No: 3 Standard calibration curve of Indomethacin at pH 6.2

S. No	Concentration (µg/ml)	Absorbance
1	5	0.092
2	10	0.196
3	15	0.295
4	20	0.393
5	25	0.492
6	30	0.597
7	35	0.688
8	40	0.784
9	45	0.885
10	50	0.983

Figure No: 11 Standard calibration curve of Indomethacin



7.2 Preformulation studies [87]:

Preformulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients.

7.2.1 Spectroscopic studies [87, 88]:

1. UV Spectroscopic Analysis
2. IR Spectroscopic Analysis

(a) UV spectroscopy (Determination of λ_{max})

The light absorption in the range 200 to 800 nm of a solution buffer it exhibit a maximum only at about 319 nm.

(b) Raw material analysis of Indomethacin USP [86]:

Raw material analysis of Indomethacin was carried out using Fourier Transform Infra red spectrophotometer (FTIR) by KBr pellet method.

7.2.2 Particle size distribution of Indomethacin powders [67]:

The particle size measurement of indomethacin micronized powder was determined by using a (Mastersizer-2000) particle size analyzer. An appropriate amount of indomethacin powder was added into the analyzing chamber containing deionized water as the medium. A few drops of Triton solution (1% w/w) were added to disperse the powders. Test results of the type of powder were recorded. In addition, this powder was examined under a microscope with a magnification of 400X**.**

7.2.3 Compatibility studies of Indomethacin and formulation components:

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and not affecting the shelf life of product or any other unwanted effects on the formulation. The physical mixture of drug & polymers were used for determination of Infrared spectrums.

7.2.4 Physical observation [54, 79]:

The active ingredients were mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in cleaned and dried vial in stability chamber at 25°C/ 60% RH & 40°C/ 75% RH. Physical observation has been carried out visually for 0, 2 and 4 weeks.

7.3 Formulation development:

Study involves formulation of an extended release Indomethacin drug loaded pellets, release over an extended period of time.

Selection of Process

Pellets were done by Fluid bed processor (FBP).

General procedure for formulation of extended release pellets:

Preparation of drug layering solution:

- Required quantity of isopropyl alcohol was taken into a suitable vessel and to it ethyl cellulose 4cps added and stirred well to get clear solution. This process was done at room temperature.
- To the above solution purified water, sodium lauryl sulfate and hydroxy propylcellulose were added slowly under continuous stirring to dissolve completely.
- Then Indomethacin was added slowly under continuous stirring to get a uniform dispersion. After attaining uniform dispersion talc was added immediately with continuous stirring for not less than 30 min.
- The above dispersion was passed through #40 sieve and complete dispersion was passed.
- Dispensed sugar spheres were loaded into wurster column and the process started with present parameters to adjust the fluidization.
- The dispersion was sprayed onto sugar spheres at inlet temperature of 40±5°C and bed temperature of 35 ±5°C then spray rate increased slowly to optimum rate.
- The drug layered pellets was dried for not less than 15 min with low fludization at a bed temperature of 40±5°C and weight gain was checked.
- The drug layered pellets were passed initially through #20 sieve and the twins retained on the sieve were removed. Again they are passed through #30 sieve and the passed drug layered pellets were discarded.
- The pellets were stored in suitable air tight container.

Extended release coating:

- Extended release coating solution in which polymer concentration 1:1 ratio was prepared (5%, 7% and 9%) weight build up was noted.
- Required quantity of isopropyl alcohol was transferred into a suitable vessel at room temperature to that ethyl cellulose 4 cps, purified water, hydroxypropyl cellulose was added slowly under continuous stirring until it dissolves completely.
- The drug layered pellets were loaded into wurster column and the process started with present parameters to adjust the fluidization.
- The solution was sprayed onto drug layered pellets at inlet temperature of 40±5°C and bed temperature of 35±5°C then spray rate increased slowly to optimum rate.
- The extended release coated pellets was dried for not less than 30 min with low fluidization at a bed temperature of 40±5°C and weight build up was checked
- The extended release coated pellets were passed initially through #20 sieve and the twins retained on the sieve were removed. Again they are passed through #30 sieve and the passed drug layered pellets were discarded.

Lubrication

- The talc was passed through #40 sieve and pellets were lubricated.

7.3.1 Parameters in capsule:

Table No: 4

Capsule shells	Green opaque cap/clear transparent body size 1 empty hard gelatin capsule shell imprinted with X08 on both cap and body with black ink.
Description	Green opaque cap/clear transparent body size 1 hard gelatin capsule shells filled with pale yellow pellets & imprinted with X08 on both cap and body with black ink.

7.3.2 Parameters maintained in fluid bed processor:

Table No: 5

Machine type	Pam Glatt 1.1
Material nozzle diameter	0.8 mm
Number of guns	01
Spray mode	Continuous
Inlet air temperature	50±10°C
Product temperature	40±5°C
Exhaust temperature	40±5°C
Atomization	2-3 bar
Air flow	600 -750 m/sec
Drive speed	55-65%
Peristaltic pump speed	08-12 rpm

Table:6: 7.3.3 Formulation chart of Indomethacin pellets:

Drug layering

S. No	Ingredients	Quantity per unit (mg)					
		F-1	F-2	F-3	F-4	F-5	F-6
1	Indomethacin	75	75	75	75	75	75
2	Ethyl cellulose (4cps)	5	5	5	7	5	5
3	Povidone K30	20	-	-	-	-	-
4	Hydroxypropyl Cellulose, Low-substituted	-	20	-	-	-	-
5	Hydroxypropyl Cellulose	-	-	20	18	20	20
6	Sodium lauryl sulfate	0.5	0.5	0.5	0.5	0.5	0.5
7	Talc	1	1	1	1	1	1
8	Sugar spheres (500-600 µm)	217.5	217.5	217.5	217.5	217.5	217.5
9	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
10	Purified water	q.s	q.s	q.s	q.s	q.s	q.s

Extended release coating

S. No	Ingredients	Quantity per unit (mg)					
		F-1	F-2	F-3	F-4	F-5	F-6
11	Ethyl cellulose (4cps)	8	8	8	8	11	14
12	Povidone K30	8	-	-	-	-	-
13	Hydroxypropyl	-	8	-	-	-	-

	Cellulose, Low-substituted						
14	Hydroxypropyl Cellulose	-	-	8	8	11	14
15	Sodium lauryl sulfate	1	1	1	1	1	1
16	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
17	Purified water	q.s	q.s	q.s	q.s	q.s	q.s
	Extended release pellet weight	336	336	336	336	342	348
18	Talc	1	1	1	1	1	1

7.4 Evaluation of prepared pellets: [89]

7.4.1 (i) Bulk density:

Weighed quantity of 60 gms pellets was transferred into a 100 ml measuring cylinder without tapping, during transfer the volume occupied by pellets was measured. Bulk density was measured by using formula.

$$P_i = m/Vo$$

Where,

P_i = Bulk density

m = Mass of the pellets,

Vo = Untapped Volume

7.4.1 (ii) Tapped Density:

Weighed quantity of 60 gms pellets was taken into graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

$$Pt = m/Vi$$

Where,

Pt = Tapped density

m= Mass of the pellets,

Vi = Tapped volume

7.4.2 Carr's compressibility index:

Compressibility is the ability of pellets to decrease in volume under pressure. Using untapped density and tapped density the percentage compressibility of pellets were determined, which is given as Carr's compressibility index.

$$CI=Vi-V_o / Vi \times 100$$

Where,

CI = Compressibility index

Vo = Bulk density

Vi = Tapped density

Table No: 7 Compressibility index

Compressibility index (%)	Flow characters
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
> 32	Very poor

7.4.3 Hausner´s ratio

It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

Hausner´s ratio = Vo/Vi

Where,

Vo = Bulk density

Vi = Tapped density

Table No: 8 Hausner´s ratio

Flow characters	Hausner´s ratio
Excellent	1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very very poor	>1.60

7.4.4 Procedure for content uniformity: [86]

The content of one capsule was transferred into 200 ml volumetric flask, to it 100 ml equal volume of methanol and phosphate buffer (pH 6.2) was added. Then the solution was sonicated until then contents are dispersed and volume was made up with methanol and phosphate buffer (pH 6.2) in 1:1 ratio. This solution contains about 25 µg/ml indomethacin. Concomitantly the absorbance was determined 319 nm, in spectrophotometer, using the methanol and pH 6.2 phosphate buffer mixture as the blank.

By calculating the formula:

$$(TC/D)(A_U/A_S)$$

T = labeled quantity of indomethacin in mg

C= concentration (µg per ml) in the standard solution

D= concentration (µg per ml) in the test solution

Based upon the labeled quantity per capsule and the extent of dilution

Au and As are the absorbance of the solution from the capsule contents and the standard solution.

7.4.5 Capsule weight variation [55, 57]

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Capsule weight - Average weight)}}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 7.5 %

7.4.6 Percentage yield [55, 79]

The yield was determined by weighing the pellets and then finding out the percentage yield with respect to the weight of the input materials.

The formula for calculation of percentage yield is

$$\text{Percentage yield (\%)} = \frac{\text{Weight of pellets}}{\text{Weight of drug + Weight of polymers}} \times 100$$

7.4.7 Lock length [54, 79]

After filling the capsules to determined lock length in these ten individual capsules were taken from each formulation trial batch and lock length was measured manually by using vernier calipers and average of ten capsules was noted.

7.4.8 Loss on drying:

It was done in Electronic Loss on Drying (LOD) apparatus (Sartorius, Germany). Weighed quantity of 1 gm sample was placed in the pan and the temperature was increased to 105ºC and the loss on drying in % was noted.

7.4.9 IN-VITRO DRUG RELEASE STUDIES [86]:

In-vitro drug release studies of indomethacin were carried by using apparatus USP test-I rotation basket method with a stirring speed 75 rpm at 37 ± 0.5°C in 750ml of 6.2 phosphate buffer for 24 hours. 5 ml of sample, with drawn at interval of 1, 2, 4, 6, 12, 24 hours with the replacement of equal volume of dissolution media.

Filtered the solution through millipore HYLP filter and these filtrate was measured at 319 nm by UV spectrophotometer (UV-1700 SHIMADZU)

The percentages of the labeled amount of indomethacin dissolved at the time specified acceptance table.

Table No: 9

Time (hours)	Amount dissolved
1	Between 10% and 25%
2	Between 20% and 40%
4	Between 35% and 55%
6	Between 45% and 65%
12	Between 60% and 80%
24	Not less then 80%

7.4.10 Comparison of Dissolution Profile with Marketed Product

The dissolution profile (in USP 6.2 phosphate buffer) of optimized formula was compared with the dissolution profile of marketed product and the results were noted.

7.5 Kinetics of drug Release [90, 91]:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi and Peppas. Based on the R & n value, the best-fit model was selected.

1. Zero order kinetics:

Zero order release would be predicted by the following equation

$$A_t = A_0 - K_0t$$

Where,

A_t = Drug release at time 't'.

A_0 = Initial drug concentration

K_0t = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero-order release kinetics, with a slope equal to K_0.

2. First Order Kinetics:

First – order release would be predicted by the following equation

$$\text{Log } C = \log C_0 - K_t / 2.303$$

Where,

C = Amount of drug remained at time‘t’.

C_0 = Initial amount of drug.

K_t = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant ‘K’ can be obtained by multiplying 2.303 with the slope values.

3. Higuchi’s model:

Drug release from the matrix devices by diffusion has been described by following Higuchi’s classical diffusion equation.

$$Q = [D\varepsilon / \tau \,(2\,A - \varepsilon Cs)\, Cst]^{1/2}$$

Where,

Q = Amount of drug released at time‘t’.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = Solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which ‘q’ amount of drug is released.

Above equation may be simplified if one assumes that ‘D’, ‘Cs’, and ‘A’, are constant. Then equation becomes:

$$Q = Kt^{1/2}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to ‘K’.

4. Korsmeyer equation / Peppa’s model:

To study the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time.

$$M_t / M_a = Kt^n$$

Where,

M_t / M_a = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides

$$\text{Log } M_t / M_a = \text{Log } K + n \text{ Log } t$$

When the data is plotted as log of drug released Vs log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept and range was shown in the table no.10

Mechanism of Drug release as per Korsmeyer Equation / Peppa's Model

Table No.10

S. No.	N Value	Drug release
1	0.45	Fickian release
2	0.45 <n <0.89	Non – Fickian release
3	n> 0.89	Class II transport

7.6 Stability studies [59]:

In any rationale design and evaluation of dosage forms, the stability of the active component must be major criteria in determining their acceptance or rejection.

Reasons for stability studies:

- There may be chemical degradation of the active drug leading to a substantial lowering the quantity of the therapeutic agent in the dosage form.

- Although chemical degradation of the active drug may not be extensive, a toxic product may be formed in the decomposition process.
- Instability of a drug product can lead to a decrease in its bioavailability. This can lead to a substantial lowering in the therapeutic efficiency of the dosage form.

The drug release profile of batch F5 met the dissolution acceptance criteria to pass the amount of drug release test according to USP requirements. In this batch F5 was selected as optimized batches and subjected to further studies. The optimized batch F5 was charged for stability at 40°C/ 75% RH for 2 months. The drug release studies were repeated after storage for 2 months at conditions like room temperature (RT) and 40°C/ 75% RH.

8. RESULTS AND DISCUSSION

8.1 Drug- Excipient compatibility study:

Drug-Excipients compatibility study was carried out using various Excipients mentioned below table no.11. From the preformulation studies, it was observed that mixtures shown have no color change.

Table No: 11 Physical observation

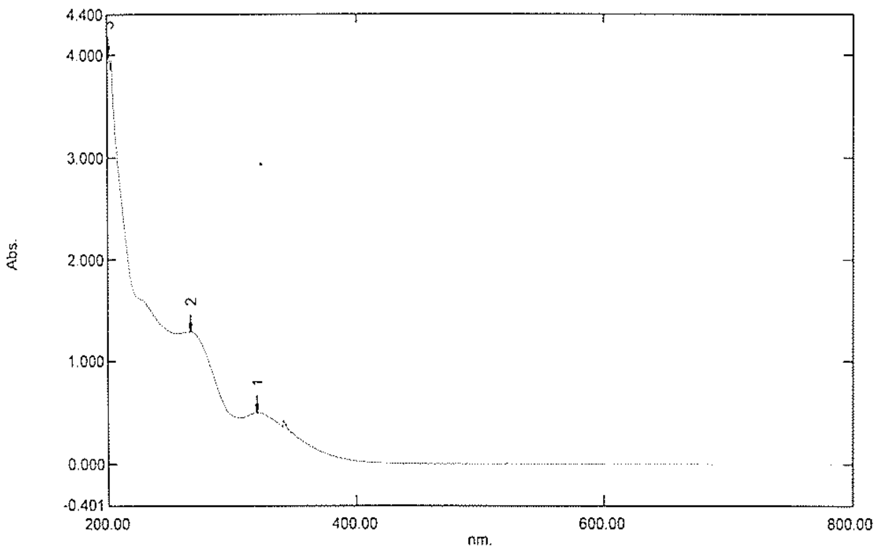
S. No	Composition details	Initial Physical Description	25°C /60 % RH & 40°C/ 75 % RH		
			1st Week	2nd Week	3rd Week
1	Indomethacin	Light yellowish Powder	NCC	NCC	NCC
2	Indomethacin + Hydroxy propyl cellulose	White to light yellowish powder	NCC	NCC	NCC
3	Indomethacin + povidone K30	White to light yellowish powder	NCC	NCC	NCC
4	Indomethacin + low substitued hydroxy propyl cellulose	White to light yellowish powder	NCC	NCC	NCC
5	Indomethacin + Ethyl cellulose (4cps)	White to light yellowish powder	NCC	NCC	NCC
6	Indomethacin + sodium lauryl sulfate	Light yellowish powder	NCC	NCC	NCC
7	Indomethacin + Talc	Light yellowish powder	NCC	NCC	NCC
8	Indomethacin + sugar spheres White to light yellowish powder	NCC	NCC	NCC	

NCC: NO COLOUR CHANGE

8.2. Spectroscopic studies:

8.2.1 UV spectroscopy (Determination of λ_{max})

Spectrum Peak Pick Report

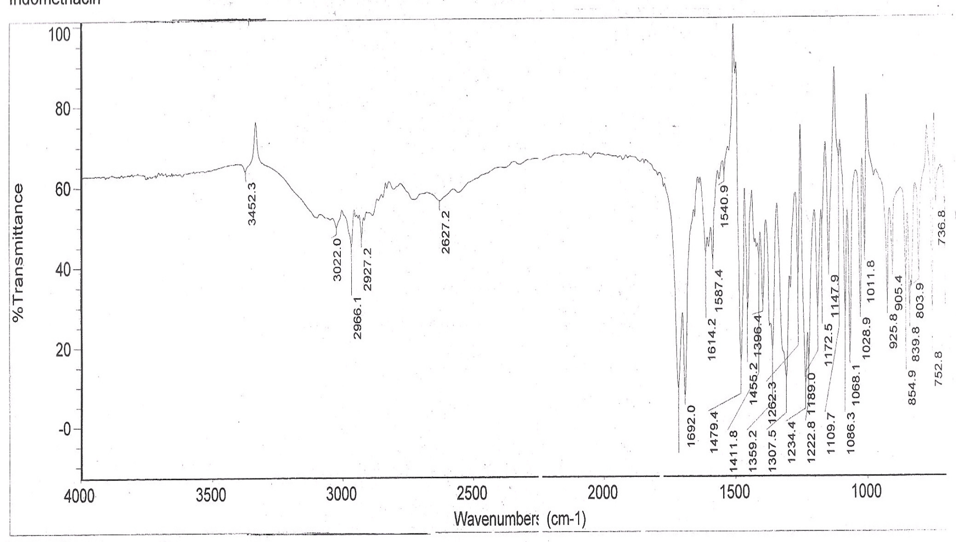


Measurement Properties	
Wavelength Range (nm.):	200.00 to 800.00
Scan Speed:	Medium
Sampling Interval:	0.2
Auto Sampling Interval:	Disabled
Scan Mode:	Auto
Instrument Properties	
Instrument Type:	UV-1800 Series
Measuring Mode:	Absorbance
Slit Width:	1.0 nm
Light Source Change Wavelength:	340.8 nm
S/R Exchange:	Normal
Attachment Properties	
Attachment:	None

No.	P/V	Wavelength	Abs.	Description
1	⊕	319.60	0.498	
2	⊕	266.20	1.296	
3	⊕	201.20	4.000	
4	⊖	306.40	0.447	
5	⊖	256.20	1.275	
6	⊖	200.80	3.975	

- The observed λ_{max} was 319.60 nm.

8.2.2 IR Spectra of drug



Number of sample scans: 64
Number of background scans: 64
Resolution: 4.000
Sample gain: 4.0
Optical velocity: 0.6329
Aperture: 17.00

FIND PEAKS:
Spectrum:
Region: 3999.6 399.2
Absolute threshold: 99.116
Sensitivity: 50
Peak list:

Position:	483.1	Intensity:	52.337
Position:	562.0	Intensity:	52.550
Position:	597.5	Intensity:	52.285
Position:	658.0	Intensity:	52.678
Position:	692.0	Intensity:	52.801
Position:	701.8	Intensity:	54.887
Position:	736.8	Intensity:	55.580
Position:	752.8	Intensity:	27.746
Position:	803.9	Intensity:	37.378
Position:	839.8	Intensity:	29.265
Position:	854.9	Intensity:	36.432

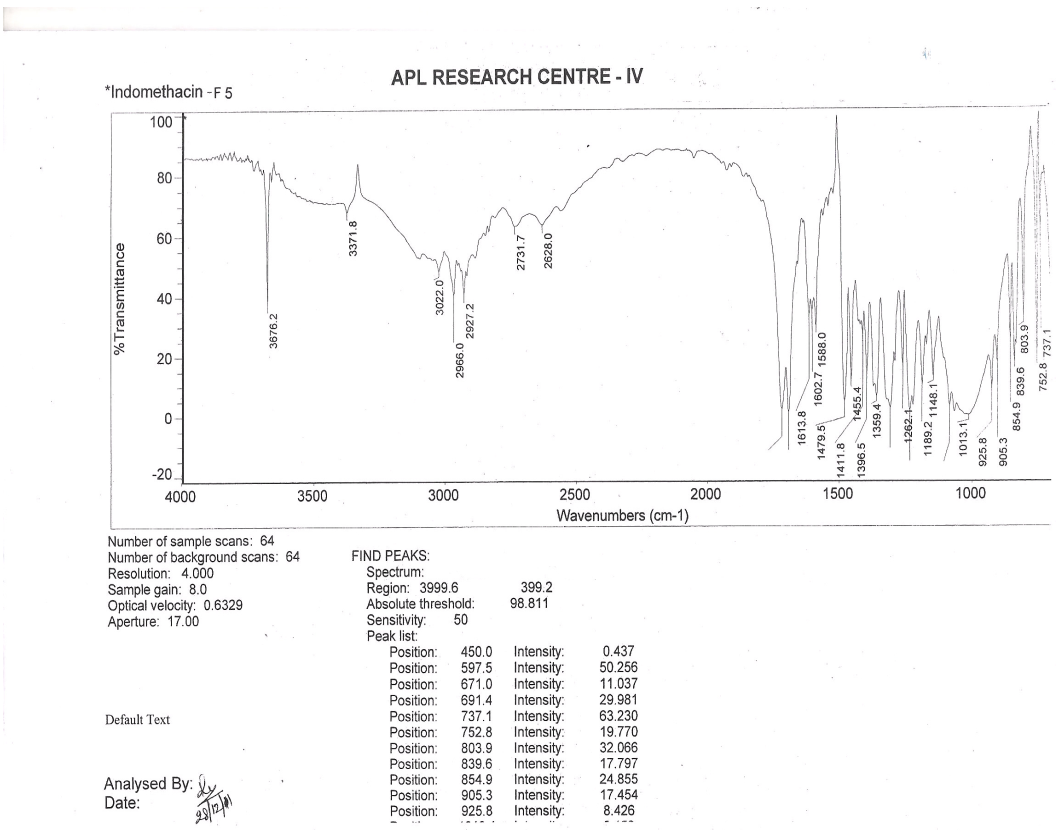
Default Text

Analysed By:
Date:

Interpretation of Indomethacin

Frequency	Groups Assigned
3452.3	O-H Stretching
3022.0	C-H Stretching
1692.0	C=O Stretching
1455.2	C=C Stretching
925.8	C-H Bending

8.2.3 IR Spectrum of optimized formulation F-5



Interpretation F-5

Frequency	Groups Assigned
3676.2	O-H Stretching
3022.0	C-H Stretching
1613.8	C=O Stretching
1455.4	C=C Stretching
925.8	C-H Bending

Discussion:

When FT-IR Spectrum of indomethacin (pure drug) and optimized formulation of Indomethacin extended release pellets (F5) were compared, there were no major changes in the position of the spectrum. So it indicates absence of physical and chemical interactions of Indomethacin extended release pellets.

8.3 Indomethacin particle size range

1

MASTERSIZER 2000

Result Analysis Report

Sample Name:
Indomethacin USP
Sample Source & type:

Sample bulk lot ref:

SOP Name:
Indomethacin USP
Measured by:
particle
Result Source:
Measurement

Measured:
Tuesday, January 10, 2012 5:00:55 PM
Analysed:
Tuesday, January 10, 2012 5:00:56 PM

Particle Name:
Indomethacin
Particle RI:
1.700
Dispersant Name:
Water

Accessory Name:
Hydro 2000SM (A)
Absorption:
0.01
Dispersant RI:
1.330

Analysis model:
General purpose
Size range:
0.020 to 2000.000 um
Weighted Residual:
1.239 %

Sensitivity:
Enhanced
Obscuration:
15.09 %
Result Emulation:
Off

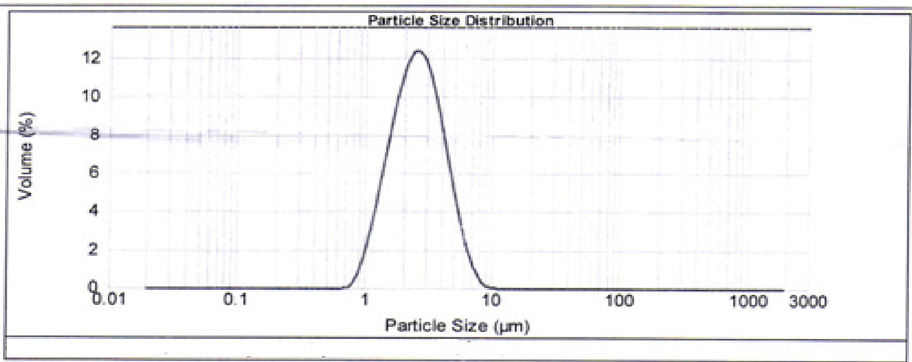
Concentration:
0.0042 %Vol
Specific Surface Area:
2.59 m²/g

Span :
1.289
Surface Weighted Mean D[3,2]:
2.313 um

Uniformity:
0.403
Vol. Weighted Mean D[4,3]:
2.849 um

Result units:
Volume

D(0.10) : 1.40 µm D(0.20) : 1.71 µm D(0.50) : 2.56 µm D(0.90) : 4.70 µm D(0.99) : 7.04 µm



Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %	Size (µm)	Vol Under %
0.010	0.00	0.105	0.00	1.096	2.72	11.482	100.00	120.226	100.00	1258.925	100.00
0.011	0.00	0.120	0.00	1.259	6.09	13.183	100.00	138.038	100.00	1445.440	100.00
0.013	0.00	0.138	0.00	1.445	11.28	15.136	100.00	158.489	100.00	1659.587	100.00
0.015	0.00	0.158	0.00	1.660	18.38	17.378	100.00	181.970	100.00	1905.461	100.00
0.017	0.00	0.182	0.00	1.905	27.24	19.953	100.00	208.930	100.00	2187.762	100.00
0.020	0.00	0.209	0.00	2.188	37.47	22.909	100.00	239.883	100.00	2511.886	100.00
0.023	0.00	0.240	0.00	2.512	48.51	26.303	100.00	275.423	100.00	2884.032	100.00
0.026	0.00	0.275	0.00	2.884	59.65	30.200	100.00	316.228	100.00	3311.311	100.00
0.030	0.00	0.316	0.00	3.311	70.13	34.674	100.00	363.078	100.00	3801.894	100.00
0.035	0.00	0.363	0.00	3.802	79.32	39.811	100.00	416.869	100.00	4365.158	100.00
0.040	0.00	0.417	0.00	4.365	86.78	45.709	100.00	478.630	100.00	5011.872	100.00
0.046	0.00	0.479	0.00	5.012	92.35	52.481	100.00	549.541	100.00	5754.399	100.00
0.052	0.00	0.550	0.00	5.754	96.12	60.256	100.00	630.957	100.00	6606.934	100.00
0.060	0.00	0.631	0.00	6.607	98.36	69.183	100.00	724.436	100.00	7585.776	100.00
0.069	0.00	0.724	0.00	7.586	99.50	79.433	100.00	831.764	100.00	8709.636	100.00
0.079	0.00	0.832	0.11	8.710	99.91	91.201	100.00	954.993	100.00	10000.000	100.00
0.091	0.00	0.955	0.86	10.000	100.00	104.713	100.00	1096.478	100.00		

Operator notes: -

Malvern Instruments Ltd.
Malvern, UK
Tel := +[44] (0) 1684-892456 Fax +[44] (0) 1684-892789

Mastersizer 2000 Ver. 5.22
Serial Number : MAL101688

File name: Lansoprazole
Record Number: 907
20 Jan 2012 3:47:54 PM

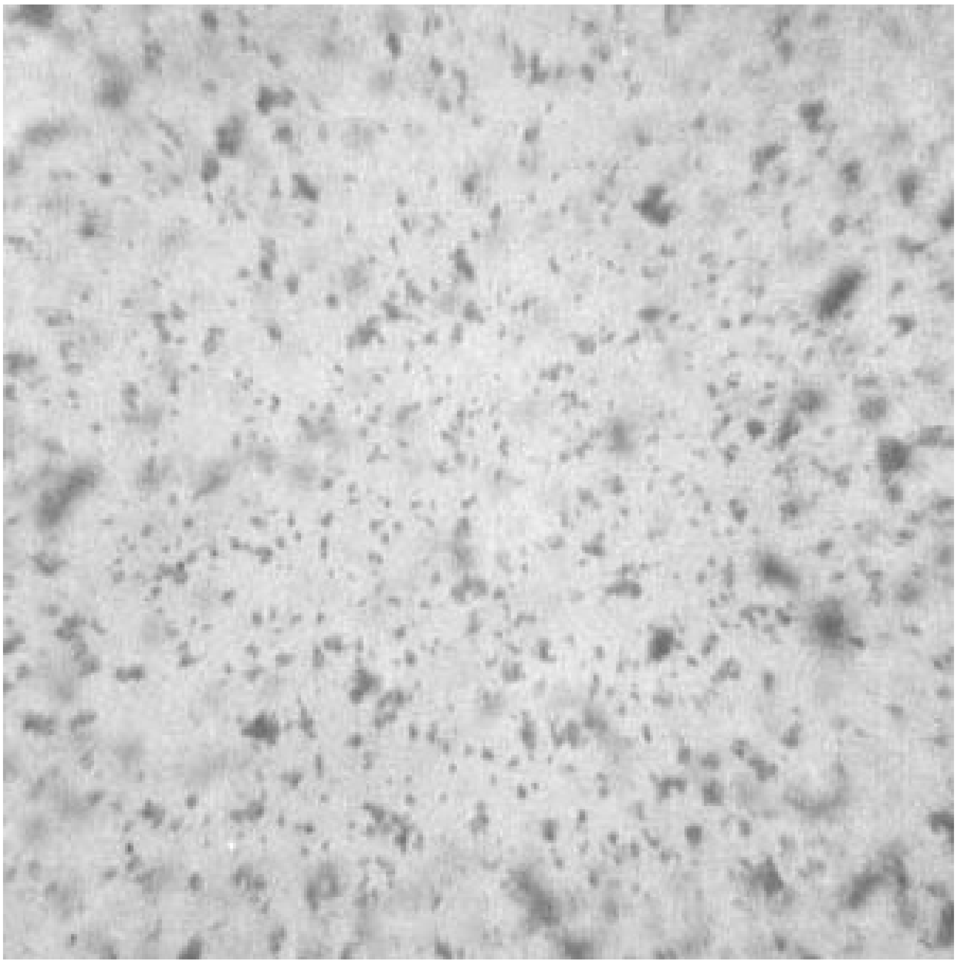


Figure No.12

Magnification of 400X

Indomethacin micronized powder

8.4 Evaluation of pellets of Indomethacin

Table No: 12

S. No	Bulk density (g/cc)	Tap density (g/cc)	Carr's Index (%)	Hausner´s ratio
F-1	0.837±0.006	0.890±0.007	6.01±1.57	1.074±0.017
F-2	0.833±0.012	0.886±0.015	6.012±0.79	1.06±0.008
F-3	0.821±0.011	0.873±0.019	5.978±0.82	1.06±0.009
F-4	0.837±0.013	0.886±0.015	5.698±0.25	1.058±0.0005
F-5	0.845±0.012	0.899±0.008	6.209±0.63	1.049±0.030
F-6	0.873±0.014	0.918±0.008	4.866±0.73	1.036±0.017

8.4.1 Bulk Density & Tap Density

Both bulk density and tapped bulk density results are shown in table no.12. The bulk density and tapped bulk density for all formulation varied in range of 0.821±0.011 to 0.873±0.014 and 0.873±0.019 to 0.918±0.008. The value obtained lies within the acceptable range and with no much difference found between bulk density and tapped bulk density. These results may further influence the pellets dissolution.

8.4.2 Compressibility Index & Hausner's Ratio

The percent compressibility of pellets was determined by Carr's compressibility index as shown in table no.12.The percent compressibility for all formulation lies within the range of 6.01±1.57 to 6.209±0.63. Hausner's ratio was found to be in a range of 1.036±0.017 to 1.074±0.017 which shows good flow property.

8.4.3 Content uniformity:

The results for uniformity of dosage units are presented in the table given below. The results were found to be within the limits (90 % to 110%). It shows that the drug was uniformly distributed.

Table No: 13

S. No	Drug layered pellets of Content uniformity in (%)	Extended layered pellets of Content uniformity in (%)
F-1	100.5 ± 0.75	99.1 ± 0.73
F-2	100.9 ± 0.66	99.4 ± 0.95
F-3	100.2 ± 0.37	99.0 ± 0.66
F-4	100.2 ± 0.45	98.3 ± 1.05
F-5	100.7 ± 1.19	99.1 ± 0.36
F-6	99.8 ± 0.16	98 ± 0.65

*Average values of the three

8.4.4 Yield & capsule lock length:

The results for yield observed NLT 96% and capsule lock length were presented in the table given below.

Table No: 14

Formulation batches	Percentage yield (%)	Capsule lock Length in(mm)
F1	99.36	19.30±0.10
F2	98.81	19.33±0.09
F3	99.47	19.35±0.10
F4	98.3	19.31±0.09
F5	98.71	19.33±0.11
F6	97.84	19.32±0.09

8.4.5 Weight variation & Loss on drying

The weight of the capsule was fixed depending up the percentage of excipients used in the each formulation .Weight variation of the prepared capsules was within the limit .Mostly, the variation was within ± 7.5%.

The prepared pellets of all the batches were evaluated for their moisture content. It is observed that the range around 1%.

Table No: 15

S. No	Weight(mg)± SD	Loss on drying(%)
F-1	409 ± 1.89	1.22 ± 0.02
F-2	409 ± 2.63	1.20 ± 0.03
F-3	409 ± 2.78	1.17 ± 0.02
F-4	409 ± 2.52	1.18 ± 0.02
F-5	415 ± 2.02	1.21 ± 0.02
F-6	421 ± 1.73	1.18 ± 0.01

*Average values of the three determinations are given as results

8.4.6 Extended release formulation of Indomethacin pellets

The *in-vitro* release studies of F1-F6 formulations were carried out by UV method and reported. The limits for indomethacin Extended release capsule as per USP are listed in the table

USP limits for drug release for indomethacin extended release capsules

Table No: 16

Time (hours)	Amount dissolved
1	Between 10% and 25%
2	Between 20% and 40%
4	Between 35% and 55%
6	Between 45% and 65%
12	Between 60% and 80%
24	Not less then 80%

Table No: 17. *In-vitro* dissolution data of F1

S. No	Time (hrs)	Amount of drug Release	% drug release	Cumulative % drug release
1	1	29.08	38.77	38.77
2	2	39.13	52.17	52.42
3	4	48.12	64.16	64.50
4	6	54.21	72.28	72.71

5	12	67.45	89.94	90.42
6	24	73.81	98.41	99.01

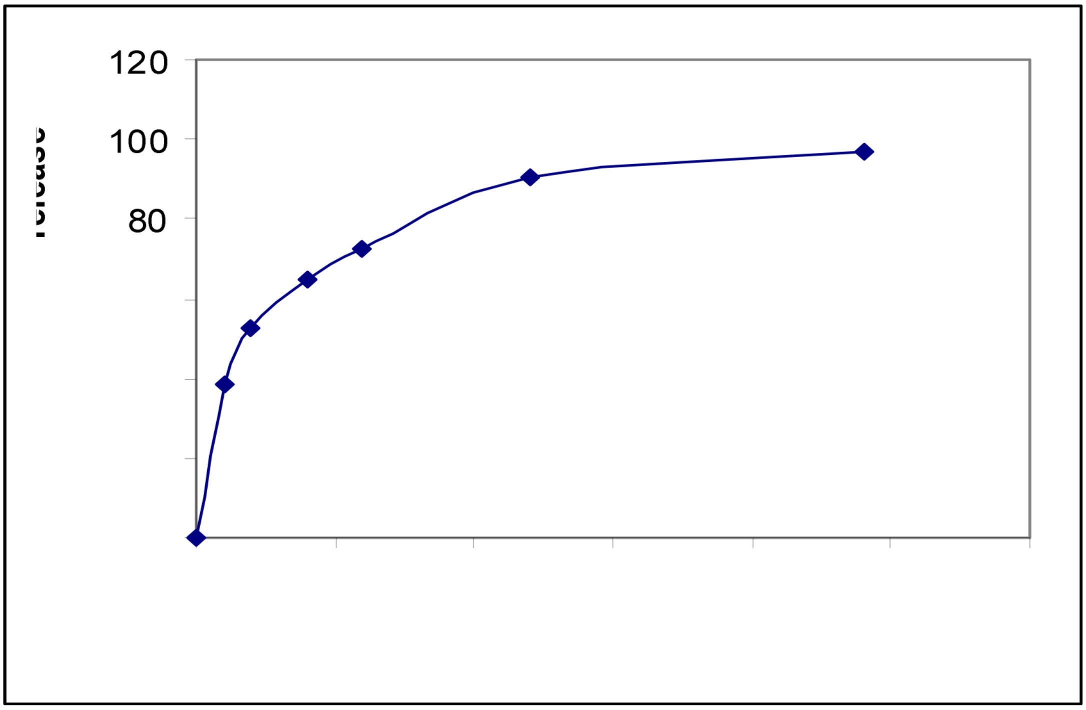


Figure No: 13. *In-vitro* dissolution data of F1

Table No: 18. *In-vitro* dissolution data of F2

S. No	Time (hrs)	Amount of drug Release	% drug release	Cumulative % drug release
1	1	27.25	36.33	36.33
2	2	35.46	47.28	47.52
3	4	45.37	60.49	60.80
4	6	53.90	71.86	72.26
5	12	61.52	82.02	82.50
6	24	72.78	97.04	97.59

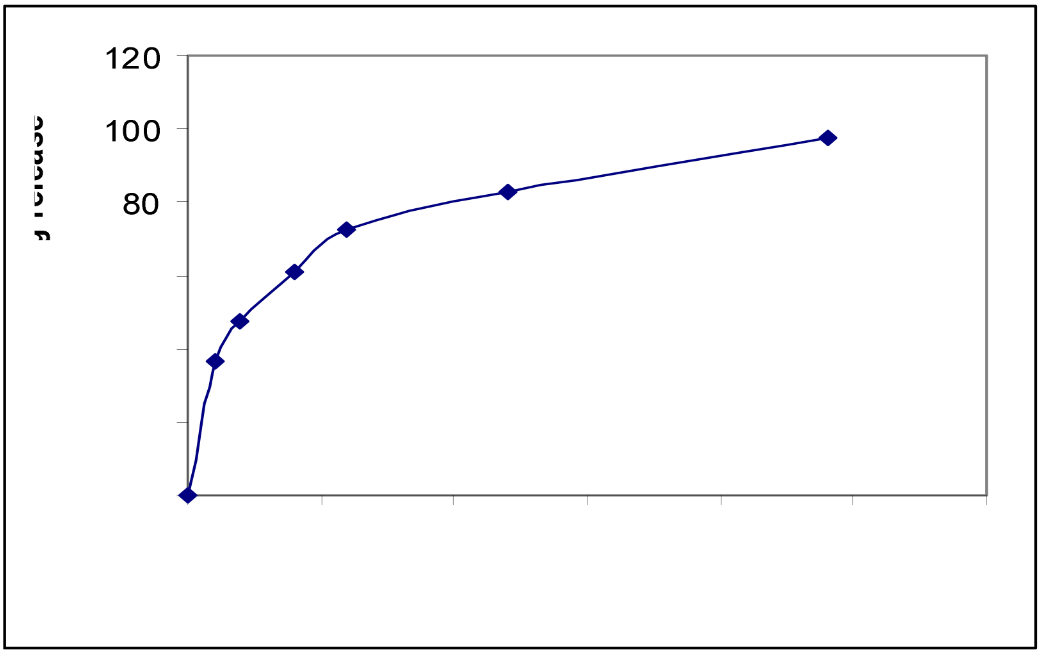


Figure No: 14. ***In-vitro* dissolution data of F2**

Table No: 19 *In-vitro* dissolution data of F3

S. No	Time (hrs)	Amount of drug Release	% drug release	Cumulative % drug release
1	1	21.62	28.83	28.83
2	2	30.76	41.01	41.20
3	4	42.10	56.13	56.40
4	6	50.55	67.40	67.77
5	12	59.54	79.38	79.83
6	24	72.93	97.24	97.77

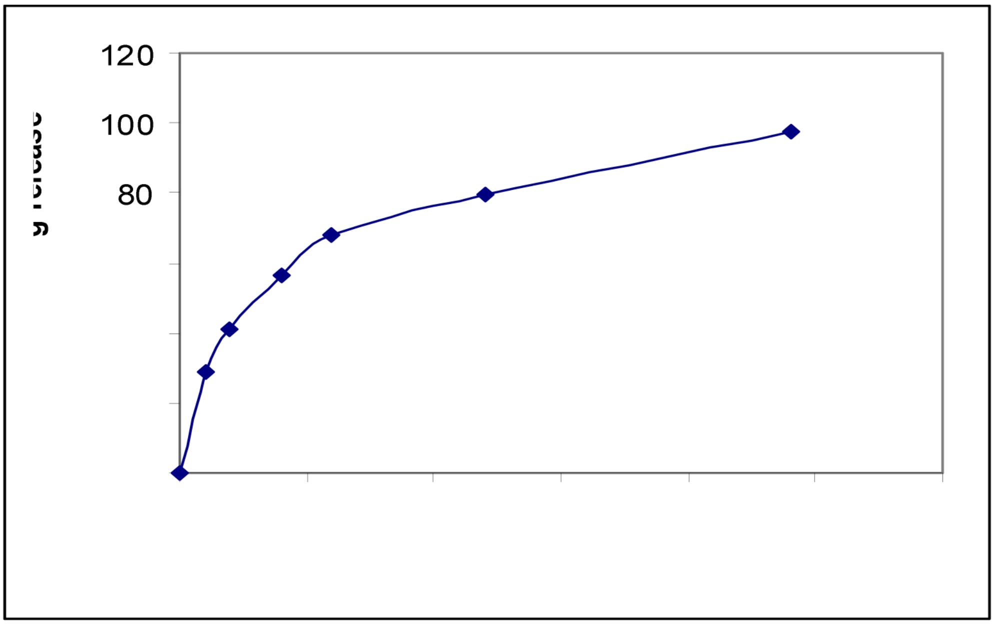


Figure No: 15 *In-vitro* dissolution data of F3

Table No: 20 *In-vitro* dissolution data of F4

S. No	Time (hrs)	Amount of drug release	% drug release	Cumulative % drug release
1	1	20.55	27.40	27.41
2	2	31.59	42.12	42.31
3	4	44.40	59.20	59.49
4	6	47.66	63.54	63.94
5	12	56.49	75.32	75.74
6	24	72.24	96.32	96.82

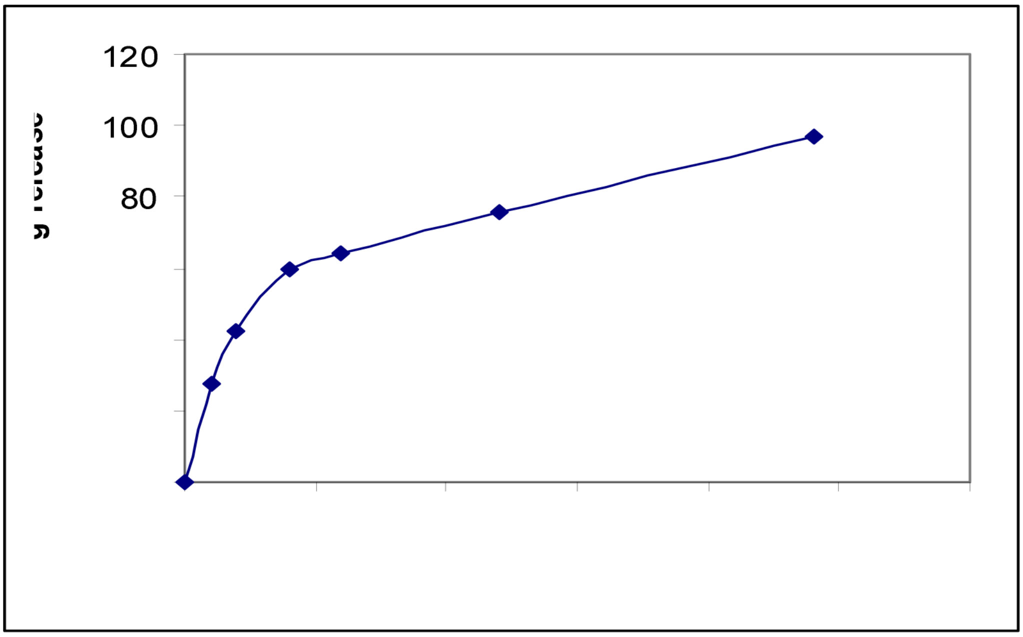


Figure No: 16 *In-vitro* dissolution data of F4

Table No: 21 *In-vitro* dissolution data of F5

S. No	Time (hrs)	Amount of drug release	% drug release	Cumulative % drug release
1	1	12.99	17.32	17.32
2	2	23.50	31.33	31.44
3	4	30.56	40.74	40.94
4	6	39.95	53.26	53.53
5	12	51.03	68.04	68.39
6	24	72.63	96.84	97.29

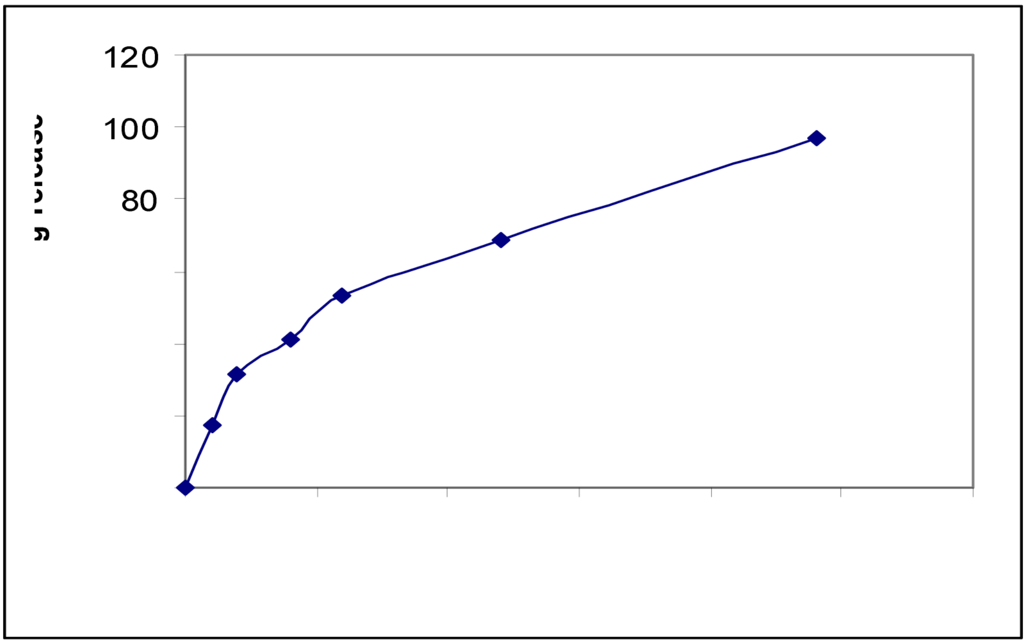


Figure No. 17 *In-vitro* dissolution data of F5

Table No: 22 *In-vitro* dissolution data of F6

S. No	Time (hrs)	Amount of drug release	% drug release	Cumulative % drug release
1	1	5.47	7.30	7.30
2	2	18.14	24.19	24.23
3	4	26.56	35.42	35.58
4	6	34.51	46.02	46.25
5	12	47.79	63.72	64.02
6	24	67.44	89.93	90.35

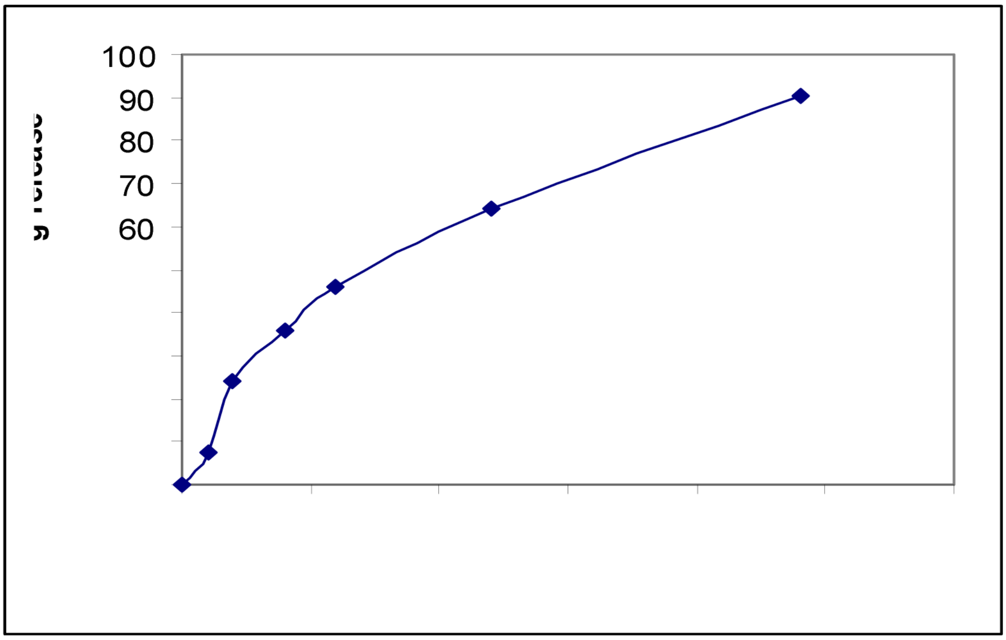


Figure No: 18. ***In-vitro*** **dissolution data of F6**

In the sugar spheres size (#30/35) was selected in the formulation used with ethyl cellulose (release retarding agent) and povidone K30 (binder), low substituted hydroxypropyl cellulose (binder), hydroxypropyl cellulose (binder), sodium lauryl sulfate (anionic surfactant), talc (lubricant) used in the extended release coating.

In the formulation (F-1) the sugar sphere size (#30/35) are coated with drug layering containing ethyl cellulose(4cps) and povidone K30 and extended release (5%) coating buildup containing ethyl cellulose(4cps) and povidone K30 (1:1) ratio. Then the dissolution parameters are observed that they were not close to the U.S.P dissolution limits. This may be due to less binding capacity the polymer.

So in the formulation (F-2) the ethyl cellulose (4cps) was kept constant and binder (povidone K30) is substituted with low substituted hydroxy propyl cellulose and the dissolution parameters are checked. In these formulation better results was observed when compared with (F-1) and they were close to the dissolution limits. But they did not exactly match with the dissolution limits of USP. This also may be due to improper binding of the polymer used.

In the formulation (F-3) the low substituted hydroxy propyl cellulose substituted with hydroxyl propyl cellulose and here also ethyl cellulose (4cps) was kept constant and the dissolution parameters are checked then the results are very close to the U.S.P dissolution limits than F-1 and F-2.

From that to obtain better results in the dissolution (F-3) consider to formulation F-4 to change in the concentration of ethyl cellulose, hydroxyl propyl cellulose in the drug layered pellets and extended release coating is kept constant. Hence a very little change was observed in the dissolution timing (6^{th}, 12^{th}, 24^{th}) hours.

Based on formulation (F-3) to formulate a further formulation (F-5) to concentration of ethyl cellulose (4cps) and hydroxypropyl cellulose was increased in extended release coating (7%) buildup in 1:1 ratio. Then the dissolution profile was checked these results were exactly matched with the U.S.P limits.

In the next formulation (F-6) the polymer concentration was increased than F-5. Here when the dissolution parameters were checked the 1^{st} hour release did not satisfy the USP limits. The further results at different interval have passed the USP dissolution limits.

From the results obtained from the above formulations it shows that the formulation F-5 is the best formulation among the all.

Figure No: 19. Optimized formulation (F-5) Indomethacin pellets

Figure No: 20. Optimized formulation (F-5) Indomethacin capsule

8.5 Comparison of dissolution Profile with marketed product

In which formulation (F-5) evaluation indicated that the dissolution profile of optimized formulation was comparable to the dissolution profile of marketed sample. It shows better release compared to market product.

Dissolution Data of Market Sample Vs Optimized Formulation (F5) in 6.2 phosphate buffer

Table No: 23

Time in hours	Ref(SANDOZ)	Optimized formulation-F5
	Cumulative % of drug release	Cumulative % of drug release
1	11.41	18.21
2	24.32	32.37
4	45.67	41.84
6	52.02	52.13
12	60.81	67.49
24	78.47	97.21

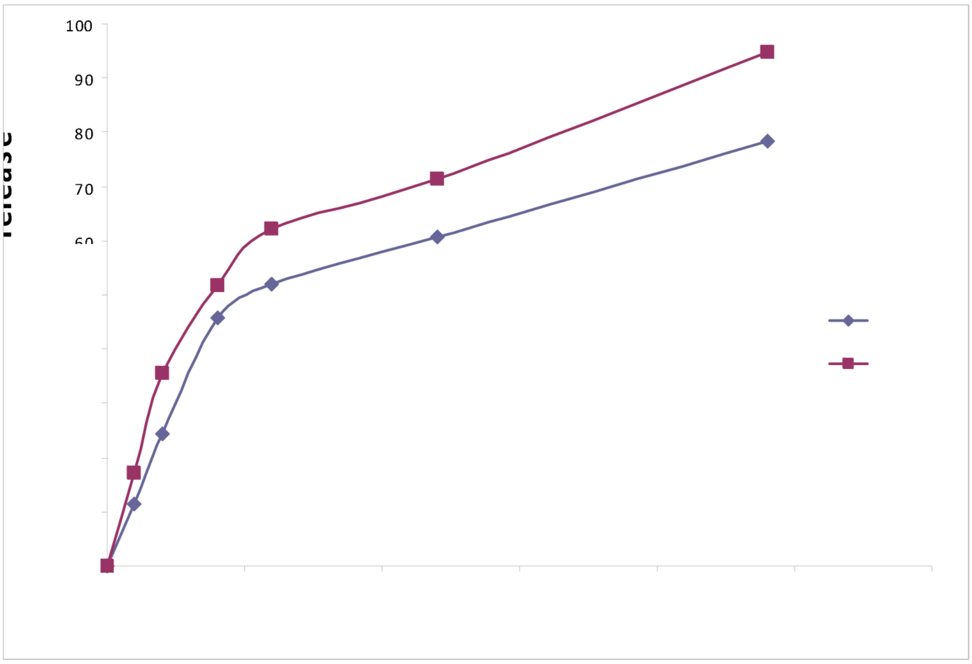


Figure No: 21

8.6 Kinetic Studies:

(i) Zero order kinetic plot

Figure No: 22

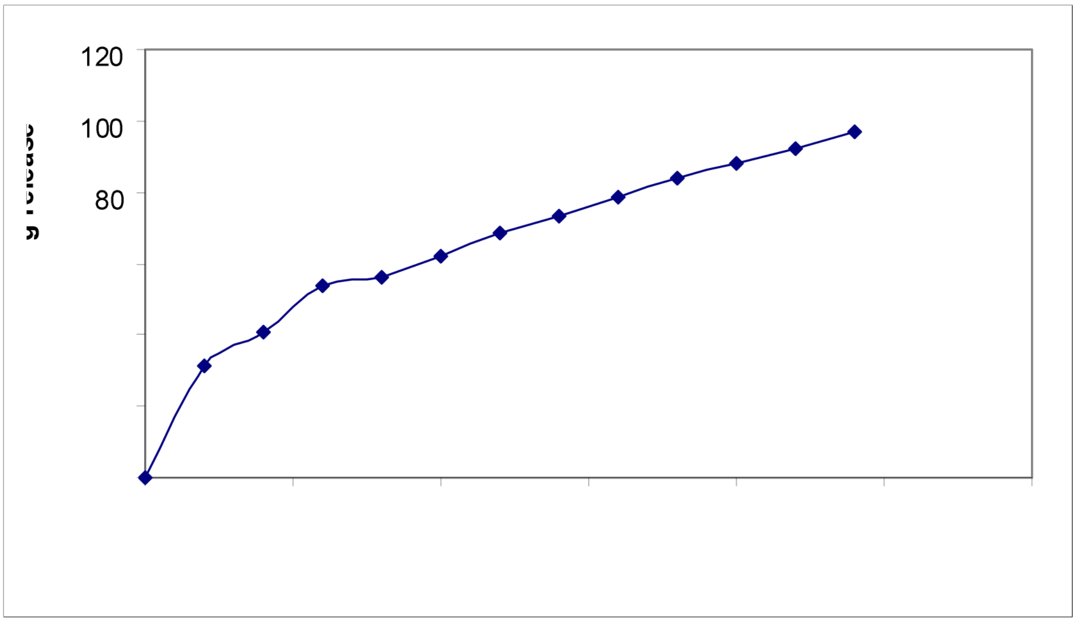


Table No: 24

Zero order
R^2
0.9796

(ii) First order kinetic plot

Figure No: 23

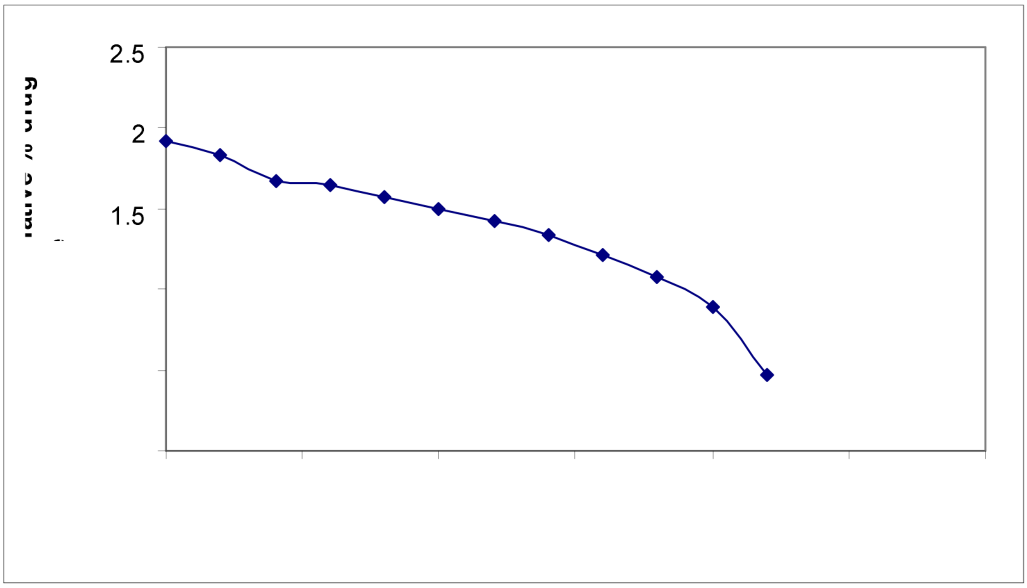


Table No: 25

First order kinetics
R^2
0.9187

(iii) Higuchi plot

Figure No: 24

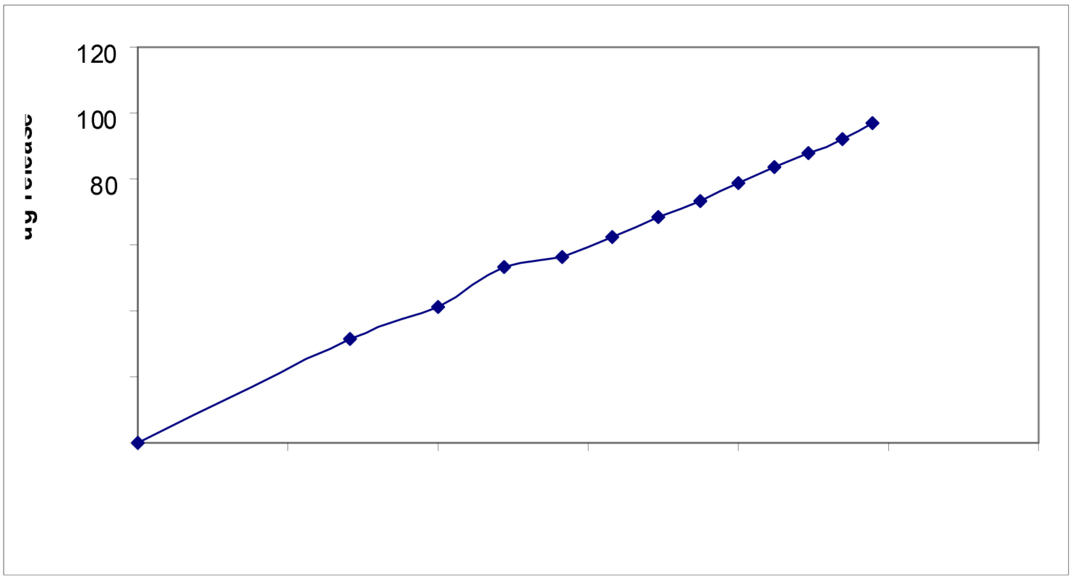


Table No: 26

Higuchi Plot
R^2
0.9958

(iv) Korsmeyer-Peppas plot

Figure No: 25

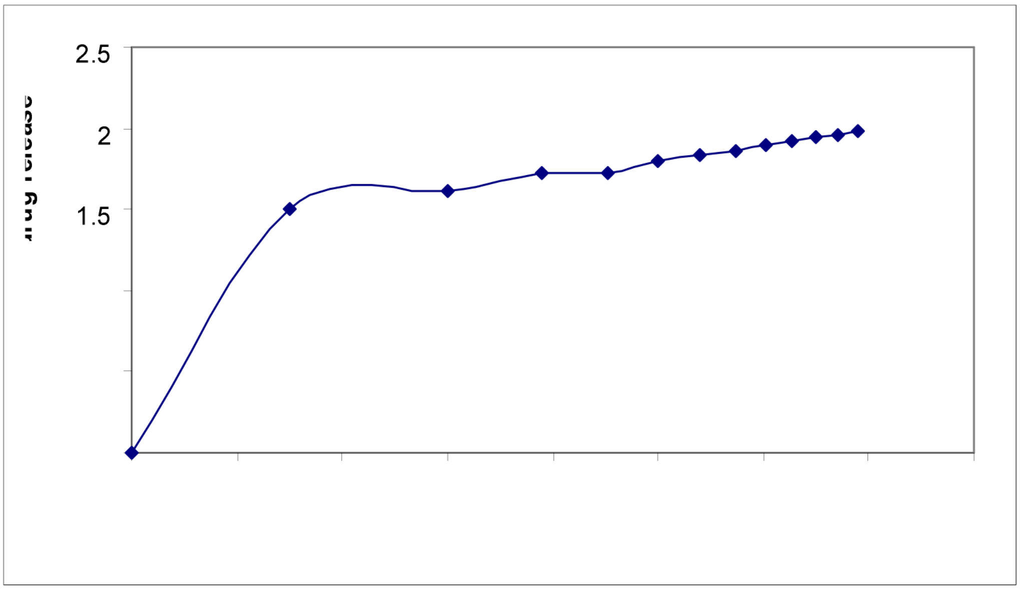


Table No: 27

Korsemeyer-Peppas plot
N
0.454

Release Kinetics study for optimized extended release pellets:

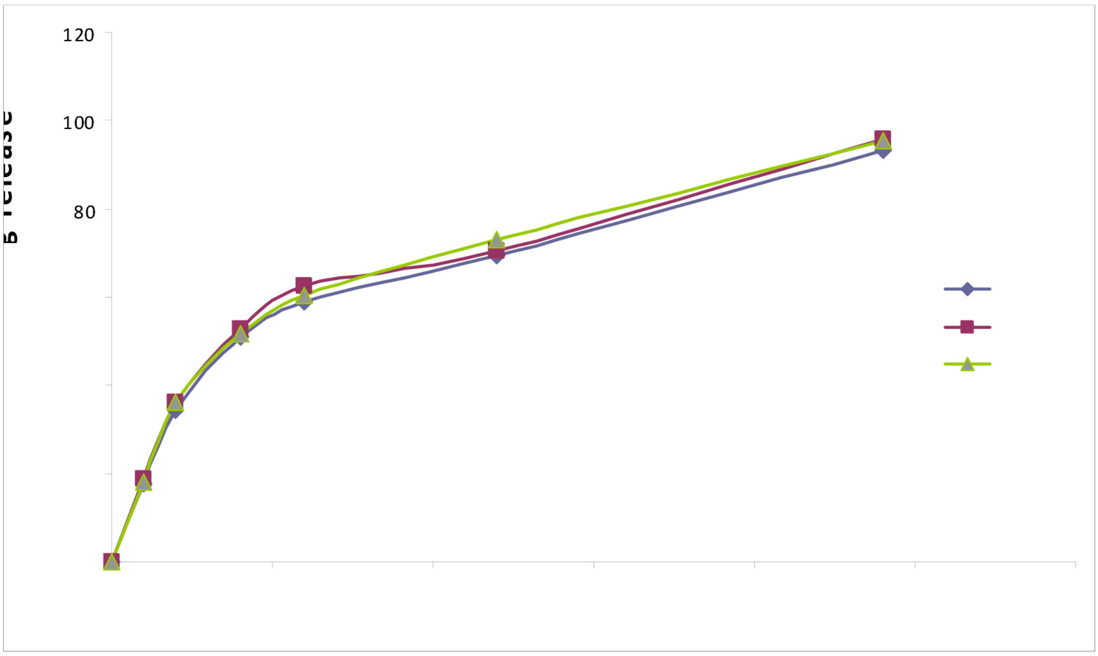
The tables and figures showed the correlation coefficient of different kinetic model for optimized (F-5) formulation. Higuchi plots were found to be of highest linearity with correlation coefficient greater than that of the zero order kinetics and correspond to that of the first order kinetics indicating that the drug release mechanism from these pellets by diffusion method. Studies revealed that release was found to be very close to zero- order kinetics with a value of 0.9796 indicating that the release was nearly independent of drug concentration. The *in-vitro* release was explained by higuchi model with a value of 0.9958 indicates a diffusion release. Moreover *in-vitro* release explained by korsmeyer-peppas equation also indicated a good linearity. The release exponent "n" was 0.454, which indicates the fickian diffusion model.

8.7 COMPARATIVE *IN –VITRO* DRUG RELEASE PROFILE BEFORE AND AFTER 1 MONTH AND 2 MONTH STORAGE AT(40°C / 75% RH.) OF BATCH F5

Table No: 28

Time in hours	INITIAL		1 MONTH		2 MONTH	
	Amount of drug release	Cumulative (%) drug release	Amount of drug release	Cumulative (%) drug release	Amount of drug release	Cumulative (%) drug release
1	12.99	17.32	12.72	16.96	14.05	18.74
2	23.50	31.45	24.03	32.15	24.85	33.26
4	30.56	40.95	30.94	41.47	30.94	41.48
6	39.95	53.54	40.73	54.58	38.91	52.16
12	51.03	68.39	49.68	66.60	53.42	71.57
24	72.63	97.03	72.63	97.28	73.84	98.93

Figure No: 26



8.7.1 DRUG CONTENT

Table No: 29

Time (month)	40°C / 75 % RH
Initial	98.4 ± 1.09
1st month	97.5 ± 1.05
2nd month	97.03 ± 0.98

*Average values of the three determinations are given as results

STABILITY STUDIES

It is observed that no variation occurs in case of dissolution profile and drug content when it is stored in 40°C / 75% RH stability chamber.

9. CONCLUSION

The present work was carried out to design and evaluate Indomethacin capsules containing extended release pellets. Indomethacin is a NSAID and is one of the most widely used drug for treating mild and severe pains.

The combination of ethyl cellulose and other polymers the drug release rate increased due to a formation of a porous on the pellets.

Formulation F-5 (containing ethyl cellulose 5% w/w and hydroxypropyl cellulose 9%w/w) showed better release profile i.e. very low initial drug release in the first two hrs and afterwards the rate of drug release increased with almost complete release of the drug being achieved in 97.03% at 24 hrs respectively. Hence F-5 release profile was passed all USP test-1 limits and further continuous for kinetic study and stability studies.

Pellets technique using ethyl cellulose as the retardant has successfully extended the release of indomethacin from its pellets formulations.

In the present study, it was found that incorporation of hydroxypropyl cellulose in the pellets not only helped to provide good initial retardation in the release but also helps to enhance the overall release rate of the drug after a suitable lag time and also it will act as suitable binding property.

The result of formulation (F-5) evaluation indicated that the dissolution profile of optimized formulation was comparable to the dissolution profile of marketed sample. It shows better release compared to market product.

Optimized formulation F-5 was subjected to data obtained from stability studies indicate that there is no much change in the release profile and drug content of pellets. Hence the prepared pellets of formulation (F-5) were found to be stable.

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